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VOLUME 35

1925

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO

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Archives of Internal Medicine

VOLUME 35

JANUARY 1925

NUMBER 1

PRIMARY CARCINOMA OF THE LUNGS*

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BOSTON

It is commonly taught that the lungs are very rarely the seat of a primary carcinoma. According to Ewing¹ it occurs in about 1 per cent of all cancers.

Adler² whose monograph on primary tumors of the lungs is so much quoted claims that in reality it is not as rare as is believed. He cites statistics given by Hansemann, who found 711 cases of carcinoma among 7790 routine necropsies 156 or 21.91 per cent, of which were not diagnosed antemortem. Of the latter sixteen or 10.3 per cent were bronchial and pulmonary tumors. Adler² himself compiled from the literature up to 1912 372 authentic cases of primary carcinoma of the lungs.

Of 1400 necropsies performed during the last ten years at the Peter Bent Brigham Hospital cancer was diagnosed in 136 instances. Of this number only five were found to be primary in the lungs. For the same period of time carcinoma (surgical and postmortem) was diagnosed in the same hospital 784 times. Therefore the relation of primary lung cancer to all cancers at the Peter Bent Brigham Hospital is 1:157.

Of 16047 necropsies performed in a large Petrograd hospital in ten years Lawrinowitch³ found sixty-one or 0.38 per cent primary carcinoma of the lungs.

Ménétrier⁴ reported six cases of primary lung cancer among 2500 necropsies performed.

At the Bellevue Hospital (New York City) during a period of twelve years (1907-1919), there were five primary lung tumors found at necropsy.

* From the department of pathology Harvard University Medical School and the pathologic laboratory of the Peter Bent Brigham Hospital

1 Ewing Neoplastic Diseases Ed 2 1922, p 808

2 Adler Primary Malignant Growths of the Lungs and Bronchi New York, 1912

3 Lawrinowitch quoted by Scott E and Forman J Med Rec 90:452 (Sept 9) 1916

4 Ménétrier Traité de Médecine Brouardel Gilbert et Thionot 1917

Cottin, Cramer and Saloz⁵ found in the Cantonal Hospital at Geneva, Switzerland (Hôpital Cantonal de Geneve), twenty-nine cases of primary carcinoma of the lungs in a period of twenty years

Of the number of 13,367 necropsies performed at the Pathologisch-Anatomischen Institut der Universität Innsbruck, Marchesani[†] found twenty-six cases of cancer (0.2 per cent) which arose in the bronchi

It is of interest to note that whereas Cottin, Cramer and Saloz⁵ found only twenty-nine cases in twenty years, they were able, later, to discover in one year eight new cases. At the Bellevue Hospital, St George⁶ discovered, in a period of twenty months (1919-1921), seven new cases of primary new growths of the lungs.

Of the five cases mentioned above from the Peter Bent Brigham Hospital two occurred in 1921, two in 1923 and one in 1924, while during the years 1913-1921, since the foundation of the hospital, no cases of primary carcinoma of the lungs were noted.

The increase in the number of primary lung cancers in the last few years is attributed by some workers to changes in the lungs, resulting from epidemic influenza.

Because of the similarity, from the clinical point of view, of primary lung cancer to any chronic lung affection, and more especially to chronic tuberculosis, a good number of these patients used to be, and are still, directed to tuberculous sanatoriums (Cases 6 and 8) where postmortems are not frequently performed. We believe the increased attention to carcinoma in general, and to lung tumors in particular, to be responsible for the increase in the last decade in the reports concerning this condition.

HISTOGENESIS

There are three elements in the lungs which may give rise to a primary carcinoma (1) the epithelium lining the bronchial mucosa, (2) the mucous glands, and (3) the epithelium lining the alveoli.

Pathologically, the three types of carcinoma are distinguished according to the gross findings and the type of cells. In rapidly growing tumors, however, the type of cells is not always a reliable criterion for the differentiation. In such cases, the combination of the clinical history, gross anatomy and histologic structure will furnish a "reasonably certain and acceptable" classification (Ewing).

In general, carcinoma arising from the bronchial lining has an alveolar arrangement and is composed of squamous or cylindrical, non-ciliated cells. In gross, the bronchial epithelium, the pleura and the parenchyma are usually involved.

[†] Marchesani. Frankfurt Ztschr f Path 27: 158, 1924.

5 Cottin, E., Cramer, A., and Saloz, M. C. Ann de med 8: 435, 1920.

6 St George, G. Proc N Y Path Soc 21: 65, 1921.

In tumors originating in the mucous glands, the structure microscopically imitates that of the mucous glands. The cells occasionally secrete mucus, and the bulk of the tumor is usually confined to the submucosa, producing early signs of bronchial stenosis.

Tumors arising from the epithelium lining the alveoli are divided by Ewing into (a) diffuse and (b) multiple and nodular. In the diffuse form, one whole lobe, or the whole lung, is uniformly consolidated, the lesion resembling organizing pneumonia or gray hepatization in croupous pneumonia. The pleura is usually involved, and local and general metastases are frequent. In the diffuse and nodular form, the air vesicles are completely or partially filled with cuboidal, cylindrical or flat cells.

ETIOLOGY

Clinical observation and experiments favor the theory that cancer is due to a chronic irritation. The development of epithelioma in areas subjected to roentgen rays, epithelioma of the lip of pipe smokers, and the soot, coal, tar and paraffin cancers are widely known.

As regards primary carcinoma of the lungs, Ménétrier affirms that "there is no primary lung cancer without a previous chronic inflammation." Statistics regarding the seat of carcinoma of the lungs and the predominant incidence in the male sex tend to confirm Ménétrier's opinion. According to Adler's statistics, the right side is the favorable location of the new growth. This is explained by the anatomic structure of the right bronchus, which is shorter, wider and more vertical in direction than the left, and therefore more prone to the penetration of foreign bodies and particles leading to irritation and inflammation. The male sex, more exposed in general to lung infections, is also more often affected by primary lung tumors. Of Adler's 372 cases, 209, or 71.9 per cent, occurred in men. In the ten cases reported here, only one occurred in a female as compared with nine in males.

Ewing believes that the tubercle bacillus is the commonest irritative factor. "The chief etiological factor of carcinoma of the lungs," says Ewing, "is tuberculosis."

The coexistence of tuberculosis and carcinoma in the same patient, whether in the lungs or in other organs, has provoked a great deal of discussion. Rokitansky (1876) affirmed that there is an antagonism between the two afflictions, a belief which was soon denied by a number of reports demonstrating the opposite. Furthermore, it has been shown that both afflictions may exist, not only in the same subject but in the same organ, whether lungs, mammary gland or uterus.

The dermatologists were first to describe the implantation of an epidermoid carcinoma on top of a lupus vulgaris, the tuberculous origin of which is beyond any doubt. It is of interest to note that in the great majority of cases, the new growth developed in the scar of a

healed lupic lesion, the scar serving as a starting point for the proliferation of the epithelium with the ultimate transformation into malignancy. In Debonnet's⁷ series of ninety cases of *lupus vulgaris*, forty-seven developed epithelioma in the scar.

Is tuberculosis the chief etiologic factor in primary carcinoma of the lungs?

Of 6,536 postmortems at the Pathological Institute at Breslau, Lubarsch⁸ found tuberculosis in 2,668, one hundred and seventeen of which, or 4.4 per cent, had cancer, and of the 3,868 nontuberculous cases, 452, or 11.7 per cent, had cancer. From the foregoing figures, it may be said that cancer is almost three times as frequent in nontuberculous cases. (This may possibly be accounted for by the fact that the percentage of nontuberculous patients reaching the "cancer age" is higher than that of tuberculous patients.)

In Marchesani's⁹ twenty-six cases of primary bronchial cancer, the new growth was in connection with cavities in nine instances, two of which were of bronchiectatic nature, and seven of tuberculous. In no instance, however, could the author find any etiologic relationship between the two conditions.

In Adler's² series of 372 cases of primary carcinoma of the lungs, there were only nineteen cases, or 5.1 per cent, with tuberculosis. Cottin, Cramer and Saloz⁵ and Cramer and Saloz⁹ reported thirty-seven cases of primary carcinoma of the lungs, six of which were tuberculous, of which two (Cases 19 and 27) developed apparently on top of a tuberculous lesion (in the wall of a cavity and in the scar at the apex). In nine cases here reported, not a single case showed evidence of a pulmonary tuberculosis.

The French clinicians Martin and Colrat¹⁰ recently, two cases of primary carcinoma of the lungs, the cause of which they believe to be syphilis.

While, in the first case described by the authors, the specificity of the lung infection was evidenced by the presence of a syphilitic gumma, and the relationship between the two conditions is suggestive, in the second, it is rather doubtful (no Wassermann test was done). The writers base their belief on the opinion expressed by Tripier¹¹ that the alveolar formations lined with a cuboidal epithelium found in a sclerosed or bronchiectatic lung which were present in this case are *new* forma-

⁷ Debonnet *Lupus et Epithelioma*, These de Paris, 1896.

⁸ Lubarsch, quoted by Claude *Cancer et tuberculose*, Actualité médicale, 1901.

⁹ Cramer, A. and Saloz, M. C. *Rev med de la Suisse Rom* **42** 160 (March) 1922.

¹⁰ Martin and Colrat *J de med de Lyon* **2** 1049, 1921.

¹¹ Tripier *Traité d'anatomie pathologique*, 1901.

tions and are due always to syphilis. This is, however, denied by practically all pathologists, who consider them as normal lung alveoli that have lost their communication with the air passages, with a result that their flat epithelium has undergone a "regressive metaplasia," taking a fetal, cuboidal aspect.

As has been noted, there is a tendency to attribute the recent increase in the number of reports of primary lung carcinoma to the epidemic of influenza, which, as it has been shown, leads to a marked metaplasia of the epithelium of the bronchi and of the alveolar lining (Goldzieher,¹² Askanazy¹³) Myer¹⁴ reported, recently, a primary carcinoma of the lung (metaplasierende Karzinom) originating in the epithelium of the right bronchus following influenza. He believes the latter to be the direct cause of the metaplasia which resulted in malignancy.

It will be seen from the foregoing that the chief etiologic factor of primary carcinoma of the lungs is unknown. It is observed that primary carcinoma of the lungs is practically always preceded by a chronic inflammatory process. Tuberculosis, as a chronic inflammation, may account for the origin of a carcinoma leading to a metaplasia of the epithelium (wall of a cavity, scar of a healed lesion) which is ultimately transformed into malignancy. Recent investigations suggest also an etiologic relationship between acute inflammation of the lungs (epidemic influenza) and malignancy.

REPORT OF CASES

CASE 1—History—A man, aged 45, a book binder, was admitted to the Huntington Memorial Hospital, March 14, 1921, complaining of inability to move the right arm, diplopia and pain in the left eye.

Late in December, 1920, the patient noticed a small, firm tumor about the size of a hickory nut, in the sacro-iliac region, to the left of the median line. The tumor was not painful on pressure, but he had pain in the sacro-iliac region when he "stooped over." Later, he began to have double vision, with pain and difficulty in moving the left eye, loss of sensation over the left side of the face and loss of taste on the left side of the tongue. His speech became thick, and he made himself understood only with difficulty. He also had slight difficulty in chewing.

Feb 24, 1921, roentgen-ray examination revealed definite bone pathology in the left ilium near the sacro-iliac joint, consistent with osteosarcoma.

March 2, the patient was operated on at the Cambridge Hospital for a swelling at the junction of the sacrum and the ilium. The pathologic report of the tumor was adenocarcinoma, secondary to some other focus.

The eye symptoms then became progressively worse, and he had greater difficulty in moving the arm. The temperature was 98-101 F.

There was a marked secondary anemia. The erythrocytic count was 1,770,000 per cubic millimeter. The hemoglobin was 45 per cent. The leukocytic count was 13,000 per cubic millimeter. The blood Wassermann reaction was negative.

On physical examination, a few coarse râles were heard in the right intra-clavicular region.

12 Goldzieher, M Cor-BI f Allg Path **26** 506, 1918

13 Askanazy, M Cor-BI f schweiz Aerzte **49** 465 (Jan 18) 1919

14 Myer, Berthold Frankfurt Ztschr f Path **27** 517, 1922

March 22, the condition in the right arm was discovered to be a fracture at the upper end of the humerus, apparently through the anatomic neck. During the last few days, the patient had been comatose a greater part of the time. He died after twenty-six days in the hospital.

The clinical diagnosis was adenocarcinoma of unknown origin.

Necropsy—The necropsy was performed at the Huntington Memorial Hospital by Dr Goodpasture, twelve hours post mortem. The body was greatly emaciated. A small convex tumor mass, measuring 2.5 by 0.5 cm, attached to the bone but not to the skin, was found over the left temple. There was an obvious fracture at the head of the right humerus. The lymph glands in the left axilla and both inguinal regions were enlarged, discrete and hard. There was no edema. The peritoneal cavity, except for the enlargement of the mesenteric lymph nodes, which contained apparent tumor, was normal.

Thorax On stripping away the thoracic muscles, definite tumor metastases were found in the fourth and seventh ribs on the right and in the second rib on the left, situated near or in the costochondral junction. These masses evidently involved the medulla and grew through the cortex. When the sternum was removed, it was found to be infiltrated with rather diffuse tumor masses which have grown, especially through the body posteriorly, and there was a large tumor, 4 by 3.5 cm, protruding into the thoracic cavity from the first left rib.

Pleural Cavities The right lung was free. The left lower lobe was adherent to the thoracic wall by firm, fibrous adhesions.

Mediastinum The lymph glands draining the left lung were enlarged, firm and infiltrated with tumor. The heart weighed 132 gm, and, except for the small size, was not unusual.

Lungs The left lung weighed 620 gm. It was quite markedly anthracotic. The upper lobe was air containing and was free, while the lower was adherent to the thoracic wall laterally and posteriorly, and to the diaphragm inferiorly. The inferior lateral two-thirds was firm and nodular. On section, its cut surfaces disclosed a tumor mass, bronchial in distribution, measuring 7 by 3.5 cm, and extending from near the hilum to the pleural surface. The tumor was fairly firm but friable, pale gray with patches of opaque yellow. The lobular structure of the lung, with pigmented septums, persisted in the tumor peripherally, but centrally the pulmonary structure was destroyed. Surrounding the tumor were many gray nodules, apparently peribronchial, giving a wider consolidation of the lung, but not uniform as is the compact tumor. The terminal bronchi were dilated and filled with thick, clear mucus. Some of the consolidated masses showed central softening, leaving small cavities resembling abscesses. The regional lymph nodes were enlarged and infiltrated with tumor. The right lung weighed 355 gm. It was pigmented and air containing. There was no evidence of tumor or inflammatory consolidation in the lung.

Larynx, trachea, and alimentary canal appeared normal. The liver weighed 1,180 gm, and contained two tumor nodules, measuring 1.5 by 2 cm in diameter. The gallbladder was normal.

Suprarenals The left suprarenal was enlarged by the presence of tumor nodules in the cortex and medulla. The right was normal. Pancreas, spleen, kidneys, urinary bladder, prostate, testes and thyroid gland were normal. The aorta showed a moderate sclerosis of the abdominal portion.

Brain The fifth nerve on the left side contained a tumor nodule, 0.5 cm in diameter, situated 1 cm from the point where the nerve emerged from the brain. No evidence of tumor could be found elsewhere.

Vertebral Column Tumor masses protruded from 0.5 to 1 cm anteriorly from the bodies of the twelfth thoracic and second lumbar vertebrae. A large abscess filled with gray pus (about 50 cc) was situated beneath the left lumbar muscles and communicated with the sinus externally.

Microscopic Examination—The primary tumor was that in the left lower lobe of the lung. It involved especially the walls of the bronchi which were

infiltrated by tumor cells which had entirely replaced normal mucous membrane in places From the bronchi, it extended outward into surrounding alveoli The tumor grew as an adenocarcinoma, and in places the cuboidal or columnar cells may have contained a little mucus It was judged that the tumor originated in cells of the bronchus No evidence of cilia were found in the tumor cells The metastases were quite similar in general appearance and structure to the primary tumor

The pathologic diagnosis was primary carcinoma of the lung (left) with metastases to the liver, suprarenal, bones (extensive) and fifth nerve, and arteriosclerosis

The early and extensive metastases to the bones is of interest in this case The bodies of the involved vertebrae were extensively infiltrated with adenocarcinoma, even though there was no outward change in the structure It is also of interest to note the invasion by tumor of the fifth nerve and of the lymph glands in the left axilla and in both inguinal regions

CASE 2—History—A man, aged 44, an Armenian, entered the Peter Bent Brigham Hospital, March 3, complaining of pain in the abdomen and chest The family and the past histories were negative Two and a half months before, he began to suffer from pain in the abdomen radiating to the chest, associated with belching of gas At the same time, he began to lose weight and strength

Physical examination showed him to be undernourished and cachectic The heart was negative The lungs were normal except for dulness over the left chest anteriorly and diminished breath sounds over that area In examination of the liver, dulness increased from the fourth space to 6 cm below the costal margin The lower border of the liver was distinctly felt It was smooth, firm and moderately tender In the median line, just above the lower border, a definite irregularity could be felt in the surface of the liver The rest of the physical examination was negative

The blood Wassermann reaction was negative The stool was positive for bile Urine examination gave negative results The hemoglobin was 80 per cent The erythrocytic count was 5,056,000 per cubic millimeter The leukocytic count was 9,800 per cubic millimeter The temperature was 99-100 F

Roentgen-ray examination of the chest in a lateral position, on admission, showed the tumor mass to arise in the anterior mediastinum The shadow somewhat overlapped the posterior mediastinum, but the posterior mediastinum was essentially clear

Roentgen-ray examination of the patient's chest three weeks later showed the progress on the left side to be much more extensive It involved the whole of the lower lobe region, and there was considerable increase of the density of the root shadows on the right lung

The patient died after twenty-five days in the hospital

The clinical diagnosis was lymphosarcoma (?)

Necropsy—Postmortem examination, performed by Dr V C Jacobson, showed a well developed and emaciated white man with a slight edema of the lower extremities and scrotum The abdomen was distended and tense The liver was greatly enlarged, extending about 5 cm below the costal margin Its surface was nodular, being covered with a white, pale tumor The omentum was adherent to the anterior abdominal wall from the umbilicus to the pubis

Chest The under surface of the sternum was adherent to the entire pericardium because of the presence of innumerable grayish white tumor nodules which covered the greater part of the pericardium and pleura The lower third of the pericardial sac anteriorly was not involved in the tumor, but the other two-thirds were covered with a layer of very firm, white tumor, about

12 mm in thickness. This was continuous with a similar formation over the lower lobe of the left lung to which the parietal pleura was firmly adherent, and which was removed by removing the lung. The middle three fourths of the lower lobe was very firm, and the pleural tumor growth, and that over the mediastinum mentioned, formed a very dense mass continuous from the anterior to the posterior surfaces. The lateral quarter, while showing innumerable miliary to pea-sized nodules on its pleural surface and in its substance, contained a certain amount of air, but the tumor growth was sharply marked off from this zone. The left upper lobe showed numerous pleural metastases and subpleural growths and numerous nodules, from 1 to 15 cm in diameter, in its substance. On section, the growth was densest toward the hilum of the lower lobe, and spread out in a very irregular manner and appeared to originate in a fairly large bronchus which was considerably dilated with a rough, nodular, grayish white tumor growth which proceeded out from this into the surrounding tissue. Pulmonary veins leading from this lung were stenosed 2 cm from the hilum, and the larger tributaries in the lung were apparently filled with tumor growth. The pulmonary arteries showed also invasion by tumor. The right lung was voluminous and showed fairly marked emphysema. Here and there beneath the pleura could be felt firm, grayish red nodules, the largest 8 mm in diameter, with contracted, hyperemic borders. The lymph glands along the bronchi and trachea were slightly enlarged, only a very few of them appeared to contain any tumor. The diaphragmatic pleura on the left was studded with small tumor growths, but there was no gross extension through the diaphragm. The liver weighed 6,363 gm (14 pounds). Its surface was very irregular, due to the presence of innumerable pale white, firm tumor nodules streaked with red, which varied in size from 2 mm to 8 cm. They formed rounded, rosette-like projections below the capsular level. There was no obstruction of the portal vein, inferior vena cava, hepatic artery or the main trunks of the hepatic vein. Incision longitudinally showed two very large tumor growths in the right lobe, the largest being 19 cm in diameter. There was very little parenchyma remaining, the tumors being so numerous. In some parts, the location of portal spaces was striking, but it was difficult to ascertain, in the gross, how the tumor reached the liver. Many hepatic veins were invaded, and implantations on the intima were quite numerous in the finer branches. There was some dilatation of the bile ducts, but no remarkable bile staining of the parenchyma and none of the tumor. The lymph nodes at the head of the pancreas and along the bile ducts were found to be invaded by tumor. The other organs, except for the right kidney in which a leiomyoma was found, were not remarkable.

Microscopic Examination.—Lungs. Sections taken from the region of the primary growths showed the following features. The most striking characteristic was the extensive infiltration by the tumor cells, forming a conglomerate new growth. One section showed the alveoli filled with round or oval tumor cells with dark-staining nuclei, and in some areas there was a large mass of necrosis. There was also considerable connective tissue proliferation throughout, and in some areas much small cell infiltration. Some of the blood vessels and alveoli showed a moderate amount of carbon deposit. Many bronchioles and small blood vessels were filled with the same epithelial tumor cells. Lymph glands were firmly adherent to all the surrounding structures and represented a rich tumor cell infiltration with a certain amount of tissue reaction. The section of the bronchiolar wall showed clearly the origin of the tumor. It arose from the epithelium of the mucosa and not from the tubulo-alveolar glands, which, as a whole, were quite normal except for degenerative changes in places, due to pressure of the surrounding tissue. The neoplastic change in the mucosa made the latter about six times its normal thickness. The cells had broken through the muscle wall and between cartilage spaces. The surrounding alveoli were filled with tumor, and invasion of blood and lymph stream had occurred. The small size of the tumor cells was noteworthy. Mitotic

figures were abundant. No ciliated cells were seen. The pleura was greatly thickened. The tumor here was composed of the same type of epithelial cells as the original growth.

Liver. The tumor histology here was similar to that in the lung section. The tumor masses were encapsulated, and the larger ones were undergoing central necrosis. The other organs are not remarkable.

The pathologic diagnosis was primary carcinoma of the lung (left lower lobe, bronchial in origin) with metastases to the pleura, right lung, liver and regional lymph nodes, and leiomyoma of the kidney (right).

In this case, the tumor, originating in the bronchus, gave early metastases to the liver and possibly to the bones. (The patient had pain in the back due apparently to the presence of tumor in the spinal column, which, unfortunately, was not examined.) The new growth was composed of small columnar cells. The unusual increase in size of the liver, due to metastatic tumor was noteworthy (it weighed 6,363 gm). A remarkable thing in this case was the patient's gain in weight (from 54 to 60.4 kg), due apparently to the increase in size of the tumors during the last twenty-five days of his life.

CASE 3—History.—A white woman, aged 57, entered the Peter Bent Brigham Hospital, March 14, 1923, with the complaint of pain in the lumbar region extending down the left leg to the knee, inability to walk and weakness of the right hand. The family and past histories were not remarkable. A tumor was removed from the breast twenty-five years before.

Onset of the present illness had been with a dull, persistent, bilateral lumbar pain five months before admission. Two weeks later, the pain extended down the left anterior thigh. There also was trouble in walking and night sweats for from eight to twelve weeks (?), hemoptysis for two weeks, a spoonful in amount.

On physical examination the lungs were essentially negative. The abdomen was spastic, and the left lower quadrant was definitely tender. Several small nodules were found on the left side of the cervix. The blood pressure was systolic 110, diastolic 60.

The hemoglobin was 85 per cent, leukocytes totaled 7,000 per cubic millimeter, erythrocytes, 5,024,000 per cubic millimeter. The spinal fluid was negative. Urine examination gave negative results. Roentgen-ray examination showed an area of consolidation in the left base.

Following an operation for myoma of the uterus, the wound healed poorly, owing to infection. The patient coughed up blood tinged sputum. The temperature was of a septic character. She died after seventy-five days in the hospital.

Necropsy.—The necropsy was performed by Dr G. Hansmann. The body was that of a well developed and fairly well nourished, short female. There was an edema of the ankles and legs. The left breast was missing (There was an operative scar). The axillary and supraclavicular glands were not palpable.

Pleural Cavities.—The pleura on the left side was adherent to the base. On removing the pleura in this region, numerous tumor nodules could be seen in the intercostal muscles and below the periosteum of the rib.

Heart.—The heart, except for some warty, recent vegetation at the aortic valve, was not remarkable.

Lungs.—The right lung weighed 520 gm, the left, 580 gm. The right lung was literally speckled with small, white, creamy nodules, which varied in size from 1 mm to 0.5 cm in diameter. The peribronchial lymph nodes were not enlarged. The left lung contained a large tumor mass in the left lower lobe and in the posterior axillary line just below the interlobar fissure. The two

lobes were adherent by tumor. In this area, the lung was contracted, owing to a tumor growth which caused a puckering of the pleura. On section, the tumor mass radiated into the lung in various directions and was 6 cm in diameter. On dissecting down the bronchus to the lung, it was found that near the tumor the bronchus was definitely roughened and the tumor seemed to be present in its wall. Along the course of the bronchi and peribronchial lymphatics, numerous tumor nodules could be seen radiating to the root of the lung where very large lymph nodes were found. The largest lymph node measured 5 cm in diameter. This extended down the posterior mediastinum to the diaphragm. The nodes at the hilum of the right lung were quite normal. The liver weighed 1,335 gm., and was normally plastic and friable. However, it was speckled with tumor nodules, measuring from 2 mm to 4 cm in diameter.

Suprarenals Both suprarenals were enlarged and, on section, thin suprarenal cortex could be seen surrounding grayish tumor masses.

Brain The brain weighed 1,300 gm. In the left posterior parietal region was a tumor which arose at the site of the longitudinal sinus. It measured 15 cm in length and seemed to extend into the secondary sinuses somewhat. It was definitely adherent to the dura by clot, and its base seemed in places to have infiltrated the dura. When the calvarium was removed, it was found that in the skull, to the right of the frontal bone, was an elevated tumor mass 1 cm in diameter. When the skull cap was held to the light, it showed areas of increased and decreased density, more marked than one sees in a normal skull, and perhaps evidence of smaller, not very well defined tumors. The first lumbar vertebrae were compressed to 15 cm in width and also apparently contained tumor.

Microscopic Examination—Lungs The tumor was made up of columnar epithelium with an oval, vesicular nucleus and a deeply stained nucleolus. The cells had an adenomatous arrangement and were supported by a fine stroma. In sections taken from the bronchi, the tumor showed invasion of all of the coats. The seromucous glands, however, were intact and were surrounded by a thick wall of small, round cells. The circular muscle layer was markedly thickened. The tumor invaded largely the capillaries. An anthracosis was marked in only a few areas.

Suprarenals In the suprarenals, the tumor closely resembled that of the lungs, while in the liver the stroma was rather abundant and was dense and fibrous.

Brain The tumor was found as small nodules composed of the cells identical by their shape and arrangement to the new growth. There was an absence of any reaction to the tumor. The brain tissue seemed to have melted away before the tumor. The cells were nowhere ciliated. Mitotic figures were frequent.

The pathologic diagnosis was primary carcinoma of the lungs, metastatic to the brain, bones, pleura, liver and suprarenals.

In addition to the early metastases to the bones, brain and other organs, this case was remarkable by the absence of any lung signs, on physical examination, in spite of the fact that those organs were extensively involved.

CASE 4—History—A man, aged 55, entered the Peter Bent Brigham Hospital, Oct 23, 1921, complaining of severe headaches, tinnitus of the left ear, unsteadiness of gait, projectile vomiting, difficulty in talking, hallucinations of death and Bell's palsy. He had always been healthy, up to September, 1921. The family history was negative.

The present illness began suddenly, Sept 20, 1922, when the patient was brought home from his work with a paralysis of the left side of the face. At the same time, he was disoriented to time, place and person for a few

minutes Since that time, the patient had been very restless, wandering mentally, and his speech had been thick and hard to understand A few days later, he developed hallucinations of death, and projectile vomiting

Physical examination showed an acutely emaciated man disoriented entirely as to his surroundings, time and also as to persons His face was flushed, and his eyes were bloodshot The objective findings could be summarized as follows 1 Restlessness and inability to cooperate 2 Bilateral blurring of the nasal margins of the disks 3 Protrusion of the tongue slightly to the left 4 Marked flushing of the face 5 Blood pressure—systolic, 160, diastolic, 80 6 The spinal fluid showing eleven cells and positive for sugar, negative for globulin, the blood Wassermann reaction, negative, hemoglobin, 90 per cent, leukocytes, 7,800 per cubic millimeter The temperature was normal Roentgen-ray examination of the head and sinuses did not show any abnormalities The patient died after sixteen days in the hospital

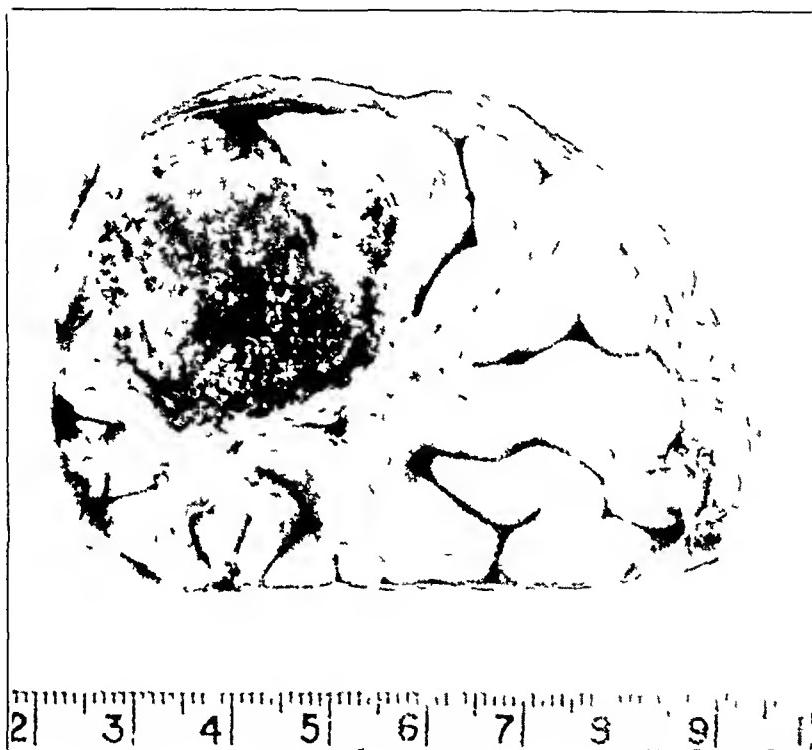


Fig 1 (Case 4)—Primary carcinoma of bronchus, metastatic tumor lying beneath the cortex at the inferior and lateral aspect of the tip of the occipital lobe

The impression was that alcoholic psychosis (?) was present

Necropsy—The necropsy was performed by Drs G Hansmann and F Fremont-Smith, six hours post mortem The body was that of a well developed and nourished male On examination externally, it did not show any pathologic condition The peritoneal cavity, except for the liver, which contained a few tumor nodules, was not remarkable

Pleural Cavities The left cavity contained 300 cc of blood tinged fluid The visceral pleura and the parietal pericardium were studded with tumor nodules A few nodules were seen in the parietal pleura The lymph nodes at the hilum were involved by tumor The pericardial cavity and heart were not unusual The heart and lungs weighed 1,410 gm The lungs were uniformly and very thickly studded with hard, gray nodules, 0.4 cm in diameter At the posterior aspect of the left lower lobe, the pleura was definitely puckered in toward the hilum When the lung was cut at this location, a gray tumor mass, 7 cm in diameter, was brought into view Some pus could be forced

out of the bronchi on pressure. The liver weighed 1,520 gm., and showed numerous small nodules, the largest being 7 cm in diameter. A small nodule was also found beneath the serosa of the gallbladder.

Suprarenals The medulla of each suprarenal was replaced by a firm, gray growth which measured 2 cm in diameter. The cortex was stretched around it, and appeared normal. The kidneys, except for a large cyst in the left kidney, were not remarkable. The other organs were normal.

Brain Tumor was found in the floor of the fourth ventricle on the right, in the right lateral ventricle on the surface of the caudate nucleus, beneath

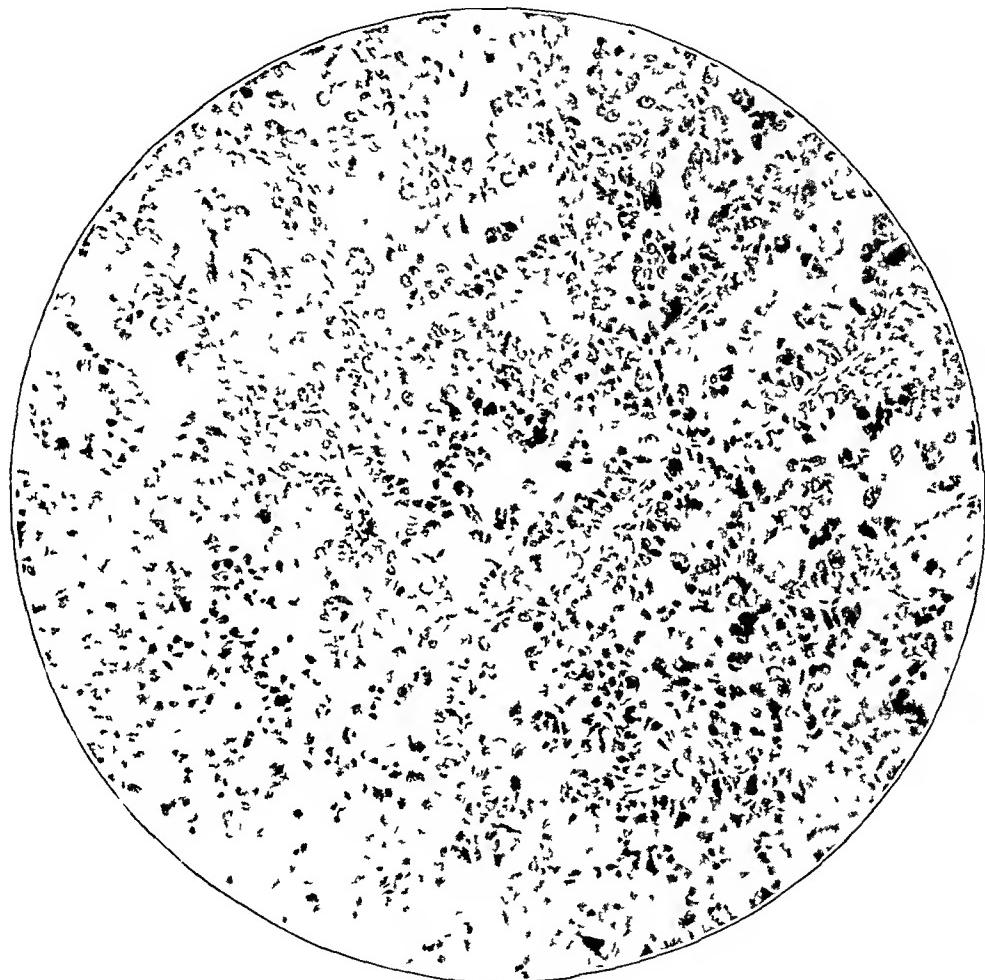


Fig 2 (Case 4)—Primary carcinoma of bronchus, tumor replacing the lining epithelium of the alveolar wall

the cortex and at the inferior and lateral aspect of the tip of the occipital lobe (Fig 1), in the center of the temporal lobe and also beneath the cortex.

Spinal Cord Lying in the meninges, surrounding the cord at various levels, but most marked at the middorsal region, were firm, whitish plaques, about 1 cm in breadth by less than 1 mm in thickness. The meninges were not adherent to the dura or to the cord at these points. Sections of the cord at various levels failed to show intramedullary metastasis. On the posterior surface of the cord just below the foramen magnum, was a plaque similar to that described, but considerably larger.

Microscopic Examination—The growth consisted of epithelial cells of the columnar type supported by a delicate stroma. The arrangement was alveolar

with some projections into the lumina. The cells varied considerably in size and shape, being, however, always columnar with a round or elongated nucleus and a centrally placed nucleolus. Mitotic figures were frequent, especially in the secondary nodules. The growth extended along the lymphatics, which were much dilated. In general, the growth was solid, but in places it seemed to replace the epithelium of the alveolar walls, and free tumor cells were frequently found in the alveoli (Fig. 2). The tumor cells did not contain cilia. The sections showed bronchopneumonia also.

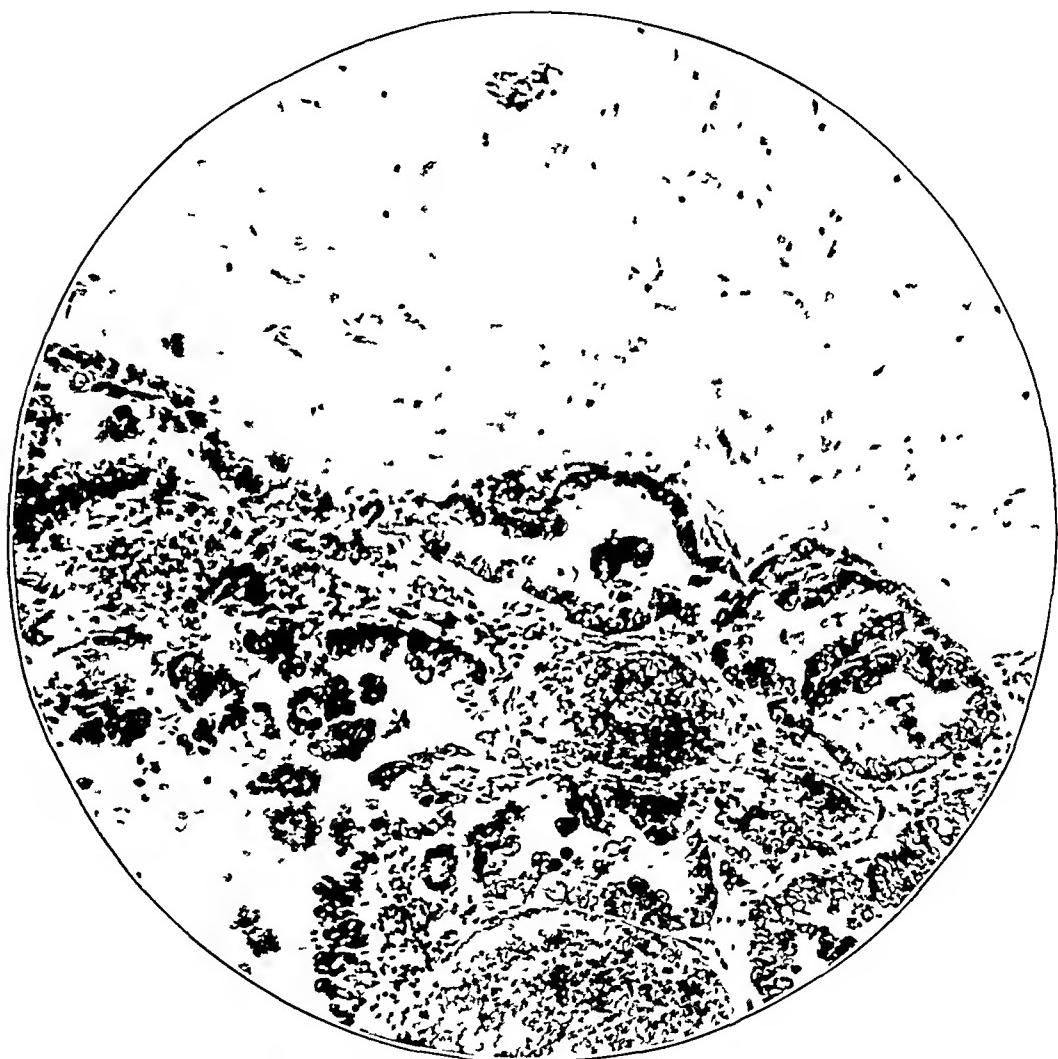


Fig. 3 (Case 4)—Primary carcinoma of bronchus, invasion by tumor of the leptomeninges

Liver and Suprarenals. The tumor resembled the primary tumor in all respects. The other organs were normal, with the exception of the kidneys which showed infectious nephritis.

Brain Sections showed the tumor lining large spaces in the leptomeninges (Fig. 3). The tumor cells showed a tendency to arrange themselves about the blood vessels and to invade the cortex along the perivascular spaces. The tendency to do so extend was a prominent feature, and the extension was to a considerable depth in places. Several sections showed a quite extensive growth within the cortex with accompanying softening of the cerebral cortex. These growths were usually not far from the meninges and could have communication with the meninges.

Cord Sections from the cord showed the same type of tumor enveloping the cord. No invasion could be demonstrated.

Dorsal Root Ganglion The tumor was compact about the nerve roots, and in one place grew right to the edge of the ganglion

The pathologic diagnosis was primary carcinoma of the lungs with generalized metastases to the brain, leptomeninges, suprarenals, liver and lymph nodes, solitary cyst of the kidney, healed infectious nephritis, bronchopneumonia, and fibrous plaques of the pia arachnoid

The features of remarkable interest in this case were The absence of any respiratory symptoms, the sudden onset of the disease with brain symptoms, and the unusually extensive metastases (brain, leptomeninges, pleura, liver, suprarenals and lymph nodes) The tumor grew in solid masses, and in only a few areas the arrangement was alveolar The cells were columnar, and mitotic figures were abundant, particularly in the metastases

CASE 5—(The history lacks details because of the patient's poor knowledge of English and lack of cooperation) K L, a man, aged 45, was admitted to the Cambridge Hospital with the complaint of severe headaches and pain in the back and neck Except for a cough for the last five years, the patient had always been well

Eight days before admission, the patient began to feel an extreme headache, which had been almost continuous

On physical examination, the left apex showed dulness with bronchovesicular breath sounds and fine râles The rest of the physical examination, except for an irregularity of the pupils (the right being larger) and an absence of abdominal reflexes, was negative

During the stay in the hospital, the patient lost power in the left hand and developed slight stiffness He died after seven days in the hospital

A clinical diagnosis was not made

Necropsy—The necropsy was performed by Dr Ash The body was that of a well developed and somewhat emaciated, white man The pleural cavities showed the right cavity to be free and the left to be obliterated in the upper third by dense adhesions The pericardial sac was free

Lungs The left lung weighed 1,480 gm and showed the upper lobe to be the seat of a large, solid mass occupying the entire lobe except for about one eighth of the parenchyma along the anterior border On section, the mass was solid and light yellow In the outer portion of the mass, the anatomic lobules were well defined, but the alveoli were apparently completely filled On the very edge, there were small, scattered nodules, and the intervening tissue was fibrosed with possibly a few remaining uninvolved alveoli The mass was apparently from one point of origin and had advanced eccentrically and uniformly, reaching the pleura over a large surface, posteriorly and laterally, but not invading it, and the interlobular surface Here, there were adhesions between the layers of interlobular pleura, but there was no invasion The pleura was distinctly thickened and, as mentioned, densely adherent, particularly posteriorly

When the bronchi were dissected to this lobe, the primary bronchus was found to be free, but the upper central division ended after a short distance blindly in the tumor mass The bronchial mucosa was completely ulcerated, and the presence of the bronchus was determined only by the cartilaginous rings The adjacent central bronchus was involved by infiltration with tumor, and a smooth, ovoid mass was present in the lumen From this gross examination, it seemed most probable that the tumor was a carcinoma arising from the mucosâ of the upper central bronchus of the upper lobe The lower lobe was crepitant and free, except for a small nodule in the lower portion posteriorly involving less than 1 cm of tissue, apparently metastatic from the

process in the upper lobe. The vessels and bronchi, except as noted above, were free. The bronchial glands on this side were distinctly enlarged, mottled yellow and black. Those under the bifurcation of the trachea also were massive from metastasis. The right lung weighed 860 gm. It was voluminous and congested. The pleura was smooth and glistening. The heart weighed 300 gm and was normal. The spleen weighed 290 gm and was enlarged and firm. The gastro-intestinal tract, liver, pancreas and suprarenals showed no pathologic condition grossly. The kidneys weighed, both, 280 gm and showed no pathologic condition. The pelvises, ureters and bladder were free.

Brain In the cerebrum, the meninges were not remarkable. The arteries at the base presented a few small plaques of intimal thickening. There were several areas of increased resistance through the cortex. The ventricles were not dilated. On serial section through a horizontal plane, the following tumor masses were found. One was in the right ascending frontal, 18 cm in diameter, involving chiefly the white matter and compressing the gray, it was well defined, light gray with a few fine red mottlings. One was in the ascending parietal, just above the middle, 1 cm in diameter and 2 cm long, parallel with the convolution, the upper portion was of a colloid appearance and involved chiefly the white and compressed the gray matter. The third was in the right occipital, 4 cm in diameter, and involved the white and compressed the gray matter just above the corpus callosum. One was on the left side in the parietal lobe, 1 cm in diameter, and one on the right side, 1 cm in diameter, involving the white matter toward the mesial surface. One nodule found in the right side of the frontal lobe was situated in the white matter and touched on the gray matter of the mesial surface.

In the cerebellum, a tumor mass, measuring 1 cm by 0.5 cm, was found on the right side in the center toward the lower surface.

Microscopic Examination—Tumor of the Lung. The tumor was made up of a columnar type of cell, usually with an alveolar arrangement, and enclosing masses of cells, more pleomorphic. The cells were not ciliated. There was no mucus. There were great areas of necrosis and fat demonstrated in the necrotic cells. The tumor was extending along the alveolar spaces. The stroma was fibrous and was abundant in some areas. In the less fibrosed areas, the tumor was growing in great masses of cells, having largely obliterated the alveolar structure of the lung. The blood vessels were found to be invaded and thrombosed by tumor cells.

Bronchus One section from the bronchus, including the upper central branch of the primary bronchus of the lung, showed tumor cells growing in masses, infiltrating the submucosa. The cells here showed much less of the columnar type. Mitotic figures were more common. Another section of the bronchus showed marked infiltration of the wall with destruction of mucous glands and cartilage.

Brain The cells were of the same type, individually and in arrangement, as those found in the lung. Masses of tumor cells were here supported by a fairly well developed and quite vascular connective tissue stroma. There was considerable necrosis of the tumor in the centers of the larger masses. The striking feature was the lack of reaction in the adjacent brain tissue. For the most part, the tissue seemed to be simply melting away before the tumor. Phosphotungstic acid hematoxylin demonstrated considerable fibrin in the tumor, and there was a small amount in the adjacent brain tissue, but very little glial tissue except along the very edge of the cortex where there was a distinct zone of gliosis. While there were very few glia fibrils, there were a number of the large glial cells, usually necrotic. One section included a cyst in the subcortical tissue containing granular débris and fibrin, and lined with tumor cells, in some places single, in others piled up, particularly about the blood vessels. There was somewhat more gliosis around this lesion than in the more solid nodule. A section from the cerebellum showed the tumor to be identical to the cerebrum tumor.

The pathologic diagnosis was primary carcinoma of the left lung with metastases to the bronchial lymph nodes and the brain, and bronchopneumonia

The brain symptoms in this case also overshadowed those of the respiratory tract. The tumor in the lungs was apparently of long standing, but, on account of the patient's chronic cough (five years' duration), no particular attention was paid to these organs.

It is remarkable that, in spite of the extensive involvement of the brain (cerebrum and cerebellum), the patient began to complain of cerebral symptoms only about fifteen days before death.

CASE 6¹—R. D., a man, aged 37, entered the Boston Sanatorium, complaining of a sharp girdle pain in the right shoulder and right knee. The family history was negative. The patient had neuritis, eight years before, lasting for about three months and osteoarthritis for the last five years.

About three months before admission, the patient began to feel a sharp pain in the right shoulder, followed soon by weakness and loss of weight. Six weeks later, he began to feel pain also in his right knee. He had had diarrhea for the last three months. He coughed very little and expectorated very little sputum.

Physical examination showed a well developed, slightly emaciated man. The chest was asymmetrical, the expansion being diminished on the left side. There was edema of the lower extremities. The cervical glands were palpable. The heart was normal. The lungs showed moderate dulness and bronchial breathing from the apex to the fourth rib on the right side and to the midscapula on the back (right). Bronchial breathing and a few fine râles were heard at the apex on the left side. The abdominal organs and prostate were negative. The bones showed chronic hypertrophic osteoarthritis. The reflexes were normal. The temperature was around 100 F in the afternoons.

During his stay at the sanatorium, the patient developed pain along the spine and in the forearm. For the last week, he was delirious. He died three months after admission.

The clinical diagnosis was pulmonary tuberculosis, chronic osteoarthritis, blepharitis, tinea versicolor.

Necropsy.—The body was that of a moderately emaciated, white man of tall stature. The upper part of the chest and lower part of the abdomen were covered with branlike scales (tinea versicolor). Just over the inner tuberosity of the right femur, a soft mass was felt which seemed to contain particles of bone. Pleural cavities showed the left to be obliterated by adhesions at the very apex and in the lateral upper portion of the lower lobe. The right was obliterated at the apex and for about 0.5 cm below laterally. The heart was normal.

Lungs. In the right lung, the pleura was smooth except over the posterior portion of the upper and adjacent upper fourth, where it and the parenchyma were torn in breaking adhesions. The parenchyma was crepitant through the entire middle lobe, the anterior half of the upper lobe and all but the upper posterior fifth of the lower lobe. This excluded tissue was the seat, in the anterior portion, of a uniform infiltration. On cut surface, the tumor was grayish red with small, yellow mottling. It was firm. This tissue was continuous in the two lobes through the interlobar pleura. From the apex was shelled out a well circumscribed, white, firm mass, 1.5 cm long and 1 cm in diameter. The tissue behind this firm mass was red, necrotic, rather pulpy and largely ulcerated away to form a very irregular, indefinite cavity with

15 This case was reported from the point of view of osteoarthritis by Dr Edwin A Locke Arch Int Med 15 659 (May) 915

granular walls and without any fibrous reaction. The overlying parietal pleura was infiltrated with tumor. The ribs were not involved. The remainder of the parenchyma was dark from pigment and richly supplied with blood. The mucosa of the bronchi was deeply congested, the vessels were free and the glands anthracotic. The left lung was voluminous but not heavy. The pleura, except at the apex where it was adherent to the chest wall, was smooth and glistening. The lung parenchyma was deeply pigmented black, generally vesicular and crepitant throughout except for three small masses in the lower lobe. The largest was just beneath the point of the pleural adhesion. The second was located anteriorly toward the base, and the third was deep in the parenchyma. The cut surface of the lungs was dark and moist. The mucosa of the bronchi was congested. The vessels and lymph glands were free from tumor.

Kidneys. The left kidney showed at the upper pole anteriorly a firm tumor nodule, measuring 2 cm in diameter, which apparently did not involve the medulla. The cut surface of the kidney was generally pale. The cortex averaged 5 mm. The markings were fairly distinct. The right kidney was not unusual. The spleen showed chronic tumor. The liver showed passive congestion. The gastro-intestinal tract was free throughout. The pancreas, suprarenals and prostate were normal.

Knee. In the right knee, the tumor felt through the skin measured 6 by 3 by 3 cm, and was covered by thickened periosteum. It was situated over the site of the inner tuberosity of the femur. This and the adjacent portion of shaft under the tumor were eroded to conform to its shape, and so deeply in the lower portion that the inner condyle was practically a shell. There was considerable loosely clotted blood around the tumor. The latter was not attached to the bone except by periosteum and could be shelled out of its nest in the bone without difficulty, leaving an area of porous bone exposed which was apparently not infiltrated by the tumor.

Head. The posterior end of the left internal orbital convolution was adherent to the orbital plate of the frontal bone for an area 1 cm in diameter. Where these adhesions were broken, the cortical tissue immediately beneath was soft and white, with small yellow areas of mottling. In the posterior portions of the middle frontal convolutions on both sides were areas of similar cortical softening with this yellow mottling. In posterior portions of the upper frontal on the left side was a soft area but more grayish and without the yellow. These areas were practically all of the same size, i.e., from 1 to 1.5 cm in diameter. Similar areas of cortical softening also were disclosed in the left middle occipital, posterior tip of hippocampal, left ascending parietal, upper surface, right gyrus forniciatus, right lentiform nucleus, involving a small portion of the middle of the internal capsule, lower end of the ascending, frontal and parietal convolutions that cover the island of Reil and extending into the contiguous cortex of the island, left marginal convolution, lower edge, and, finally, in the tegmentum of the pons.

Microscopic Examination.—The alveolar tissue in the right lung was displaced by tumor which consisted of columnar epithelium, the height of which depended apparently on the amount of compression. These cells formed irregular alveolar-like spaces into which projected papilla-like elements. In areas, the spaces were filled with tumor cells unattached to lining cells, much more irregular in size and shape and showing less the columnar type. There were several spaces lined with young, regular, cuboidal cells, such as are seen in the fibrosed lung, showing only in places the malignant characteristics penetration and rapid, irregular growth. No cilia could be found on any of the cells. The tumor cells accumulated in the spaces seemed to be rather of a squamous type. In one area, a thick-walled artery was found to contain tumor cells. The stroma of the tumor was of a connective tissue type, was vascular and, in areas, thick with some hyalinization. In the left lung, sections taken from a small tumor nodule showed the growth to be cellular and arranged

in nests, surrounded by a young connective tissue. The predominant type of cell here was squamous. There was in the lungs an inflammatory reaction evidenced by the presence of vacuolated endothelial cells, a number of multi-nucleated cells and polymorphonuclears. Mitotic figures were present in all sections.

Kidneys. The tumor had an adenomatous arrangement and was composed of cuboidal cells. The stroma was dense and fibrous.

Knee. In the right knee, the tumor consisted of columnar cells having an adenomatous arrangement and squamous cells gathered in nests. There was much necrosis in the sections.

Brain. Sections from four areas of cortical softening showed practically the same picture. The centers of the masses were necrotic, around this was a layer of tumor conforming closely in type of cell and arrangement to those of the parent tumor, i.e., cylindrical cells arranged either in irregular alveolar and acinar-like spaces or forming tubes about the young blood vessels forming part of the tumor. This extension along the arteries was quite striking, practically every vessel (in the tumor area) being completely surrounded by one or more layers of tumor cells. There was an occasional area in which the cells were more atypically squamous-like (Fig. 4). The tumor had its own stroma of connective tissue which in areas formed fairly thick trabeculae, covered by one or more layers of tumor cells. The areas were richly vascularized, and there was definite penetration into the surrounding brain tissue by small groups of cells. In some areas, the arrangement of young connective tissue and blood vessels resembled granulation tissue. The heart showed focal and chronic interstitial myocarditis. The liver showed chronic passive congestion, and the spleen, chronic tumor.

The pathologic diagnosis was primary carcinoma of the right lung (from bronchial mucosa) with metastases to the left lung, the left kidney, the periosteum of the right femur, and the lymph gland of the right knee, chronic passive congestion of the liver, chronic tumor of the spleen, and ossifying periostitis.

The patient's chief complaint in this case was cough and pain in the chest and pain in the knee, the last due to a metastasis. The brain metastases, as in the previous case, disturbed the patient only a short time before death. Pathologically, this case is of interest in relation to the transformation (metaplasia) of columnar cells in the tumor into squamous (in the left lung). I shall discuss this question in connection with Case 9.

CASE 7—W C N, a man, entered the hospital complaining of sore throat. The family and past histories were not obtainable. Physical examination was negative except for local throat signs. After entrance, the patient developed cough and pains in the chest, and raised purulent sputum. A blood culture at that time showed streptococci. The temperature was septic, and the white count increased. The upper third of the right chest showed signs of consolidation. Roentgen-ray examination of the chest suggested either encapsulated empyema, organizing pneumonia or neoplasm.

The patient was operated on. A solid lung was found which was tapped in all directions without obtaining pus. Following the operation, the temperature gradually returned to normal, but cough and pain in the chest persisted. There was a gradual loss of weight and strength, and the respiration became difficult. A Wassermann reaction at this time was positive, and arsphenamin and iodid were given without improvement. Six months after entrance, edema of the right arm and supraclavicular region developed. The patient died seven months after entrance.

A clinical diagnosis was not made.

Necropsy.—The necropsy was performed by Dr Stoddard. The body was that of a well developed, somewhat thin, but not greatly emaciated white man. There was edema of the right arm and right supraclavicular fossa. The lymph nodes were palpable. The pericardial cavity, the mediastinum and the heart were normal.

Lungs.—The left lung was voluminous, emphysematous and contained no consolidated areas. The right lung was adherent from the apex to the upper border of the fifth rib. The part free from adhesions was compressed so

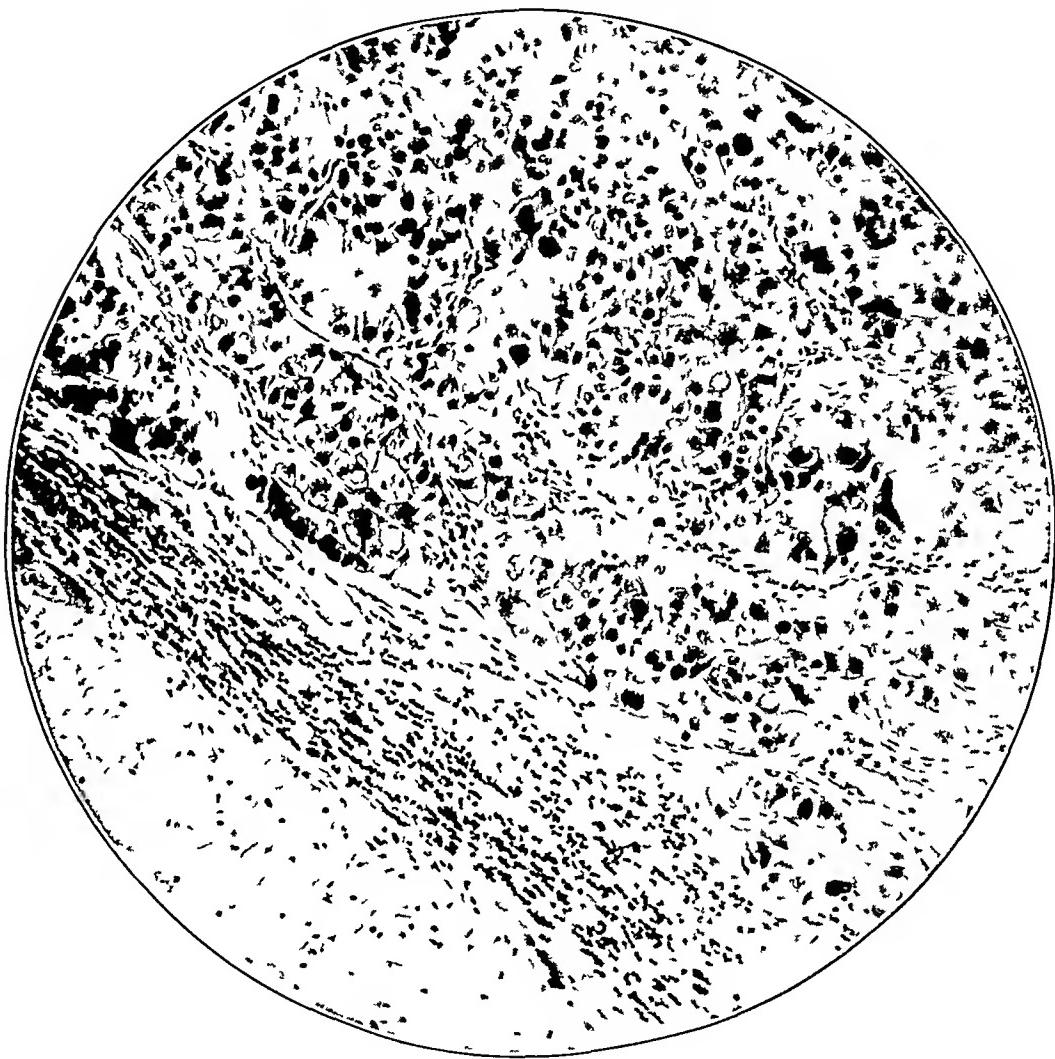


Fig 4 (Case 6).—Primary carcinoma of the lungs, metastatic tumor in the brain cortex.

that the tip of the lower lobe rested in the left pleural cavity. The upper two-thirds of the upper lobe was composed of a mass of soft material enclosed within a thickened pleura. This portion of the lung was elevated about 4 cm above the level of the lung, and appeared to be tumor tissue. On cut surface, this area was composed of soft, moderately coherent, whitish material. The center of the mass was necrotic, semifluid, pinkish white and contained small, whitish, gelatinous bits of tissue. The upper part of the lower lobe was firm and light in color. The lower part was deep red and soft. The posterior mediastinum, on dissection, showed several enlarged lymph nodes which on cut surface were pale, soft and fleshy. The other organs showed no pathology in gross.

Microscopic Examination.—Tumor Sections from the tumor showed polygonal cells with large, clear, round nuclei loosely grouped between narrow branching connective tissue septums. The cells lay either singly or in groups, with distinct spaces between the cell groups, often containing polymorphonuclear leukocytes. In many areas, the tumor cells were in all stages of necrosis. The nuclei were pyknotic and fragmented or absent, and the cell protoplasm stained deep red with eosin. Degenerated polymorphonuclear leukocytes mingled with this material. Mitotic figures were numerous. No cilia were seen in the cells. Lung Sections of the lung below the tumor area showed the bronchi and alveoli filled with polymorphonuclear cells and fibrin and endothelial cells containing blood pigment. The bronchial walls were necrotic. Lymph node A section from a mediastinal lymph node showed definite invasion by tumor cells. The spleen and liver showed passive congestion.

The pathologic diagnosis was primary carcinoma of the right lung (bronchial cell origin²) with metastases to mediastinal lymph nodes, organizing pneumonia, chronic fibrous pleurisy, lung abscess, and chronic passive congestion of the liver and spleen.

Histologically, the tumor in this case did not differ from those previously described. It metastasized only to the mediastinal lymph nodes. From the clinical point of view, the history, physical examination and the course of the disease were typical for a lung neoplasm.

CASE 8—History.—W. S., a man, aged 52, was admitted to the Boston Sanatorium, July 8, 1922, with the chief complaint of pain in the back and the left side of the chest, and cough for the last six months. The past and family histories were negative.

Six months before admission (January, 1922), the patient began to have pain in the back and in the left side of the chest, at first sharp, later dull, the pain was intermittent, lasting for about twenty minutes, and was worse on lying down, and was not related to meals or micturition. Two months later, he had a cough productive of a moderate quantity of thin, white, mucoid sputum streaked occasionally with blood. One day in March, according to the patient's statement, he had a hemorrhage, coughing up one third of a glass of bright red blood. Before entering the hospital, the patient went to several clinics, and, in April, 1922, was admitted to the Massachusetts General Hospital. His record while there was as follows:

April 3, the history of hemoptysis seemed definite, and suggested tuberculosis strongly. He had lost little weight, and had few pulmonary symptoms. The right side of the chest showed an increased whispered voice at the apex, but no rales were heard. The sputum had been blood streaked.

April 4, fluoroscopic examination revealed that the upper half of the left chest showed a marked decrease in radiability, apparently with a sharp lower border about the interlobar septum. The trachea and the heart were displaced to the left. The left diaphragm was fixed. The left apex did not light up. The right side showed considerable mottling around the root beneath the clavicle, otherwise, it was clear. The right diaphragm moved normally. The posterior mediastinum was obscured. These changes probably represented an extensive destructive and fibrosing process in the right upper lobe with retraction of the mediastinal contents to the affected side. On the left, the fine mottling suggested small bronchopneumonia areas.

April 5, clinically, the signs suggested fibrosis of the right apex with shrinkage while the right clavicle was thrown out. There was distortion of the spine, drawing the mediastinum to the right. Syphilis was excluded. There was no evidence of new growth. It was possible that there had been some chronic interlobar infection. The chances were in favor of chronic tuberculosis. The diagnosis was pulmonary tuberculosis (chronic fibroid).

April 9, the patient was discharged to the local physician.

Physical examination, at the Boston Sanatorium, July 8, 1922, showed the patient a well developed but poorly nourished man. The skin was dry, and was not jaundiced. The upper part of the chest in front was covered with tinea versicolor. The heart was negative. In the lungs, the left apex was moderately dull, with a few fine râles, in the right, there was dulness and bronchial breathing from the apex to the inferior angle of the scapula, with increased voice sounds. Below, to the base, there was flatness and a complete



Fig 5 (Case 8)—Primary carcinoma of the lungs, roentgenogram taken about ten weeks before the patient died

absence of breath sounds. In the abdomen, the liver was felt 10 cm below the costal margin with a slightly tender and somewhat nodular edge. The genitalia were negative. The prostate was not enlarged or painful on palpation. In the bones, there was right lumbar scoliosis.

July 12, the patient was tapped, and 900 cc of straw colored fluid was withdrawn from the right pleural cavity.

The urine and stools were negative. The sputum was negative on six examinations for tubercle bacilli. The patient died after nine weeks in the hospital.

The clinical diagnosis was pulmonary tuberculosis.

Necropsy.—The necropsy was performed by me, six hours post mortem. The body was that of a well developed and very poorly nourished white man, 162 cm in length. The skin had a cachectic hue. The upper part of the chest was covered with tinea versicolor. There was a slight scoliosis to the left in the region of the second and third lumbar vertebrae. The legs were slightly edematous. The pericardial cavity and heart were normal.

Lungs. The left lung weighed 1,100 gm. The organ had a normal color and was enlarged, partially covering the heart. On palpation, it had a finely



Fig 6 (Case 8).—Primary carcinoma of the lungs, anterior aspect of the right lung, *TP*, thickened pleura

granular feel, as if it were filled with very small glass beads. Between the nodules, the lung was normal, being elastic and crepitant. On section, the cut surface appeared to be peppered with disseminated, grayish nodules, from 2 to 3 mm in diameter, which gave the lung a coarsely granular feel. The mucosa of the bronchi was congested, but did not show any evidence of invasion by tumor. The vessels were not remarkable on gross examination. The right lung weighed 600 gm. The organ was contracted, and occupied only the upper part of the pleural cavity. On palpation, the lung was firm and had a somewhat beefy feel. The surface of the lung was smooth and glistening. At the apex, the pleura, which was here about 0.5 cm in thickness, was firmly

adherent to the lung, and the whole lung looked as if it were suspended in the pleural cavity by its apex (Figs 6 and 7). On section, the lung somewhat resembled a pneumonic lung in the stage of red hepatization. Scattered all over the organ, but most marked at the apex, small grayish white nodules, one-half cm in diameter, were seen. The bronchi and larger vessels were macroscopically free from any tumor invasion, and, except for a congestion, appeared normal. In some smaller vessels, grayish, pin-point elevations were conspicuous and seemed to be tumor nodules. The bronchial lymph nodes were enlarged and firm. When the left lung was removed, a tumor mass was



Fig 7 (Case 8)—Primary carcinoma of the lungs, posterior aspect of the right lung, *B*, bronchus, *P*, pericardium

found in the pleural cavity, measuring 7 by 3 by 2 cm. It had a coarse appearance, and was hard and resistant to the knife. The whole mass was situated under the periosteum of the fourth rib on the left, beginning at the junction of the latter with the vertebral column. Several small nodules of the same character were found on the same rib. The mediastinal lymph nodes were large and firm, due to invasion by tumor. The pleura, on both sides, was thickened and contained tumor nodules. The liver weighed 1,800 gm., and extended 12 cm below the ensiform process. At the lower margin of the right lobe, a tumor mass, about 6 cm in diameter, was found. The new growth was grayish white, resembling in color a freshly cut slice of bacon. In the neighborhood of the large tumor mass, and scattered all over the organ, several

small nodules, from 0.5 to 2 cm in diameter, closely resembling the main tumor, were found. The capsule of the liver did not seem to be thickened. The large veins did not contain any visible tumor masses. The gallbladder was slightly distended with bile, and its mucosa did not contain scars or ulcerations. The ducts were patent. The pancreas weighed 100 gm, and was essentially negative. The kidneys showed passive congestion. The suprarenals, gastrointestinal tract, genitalia and aorta were normal.

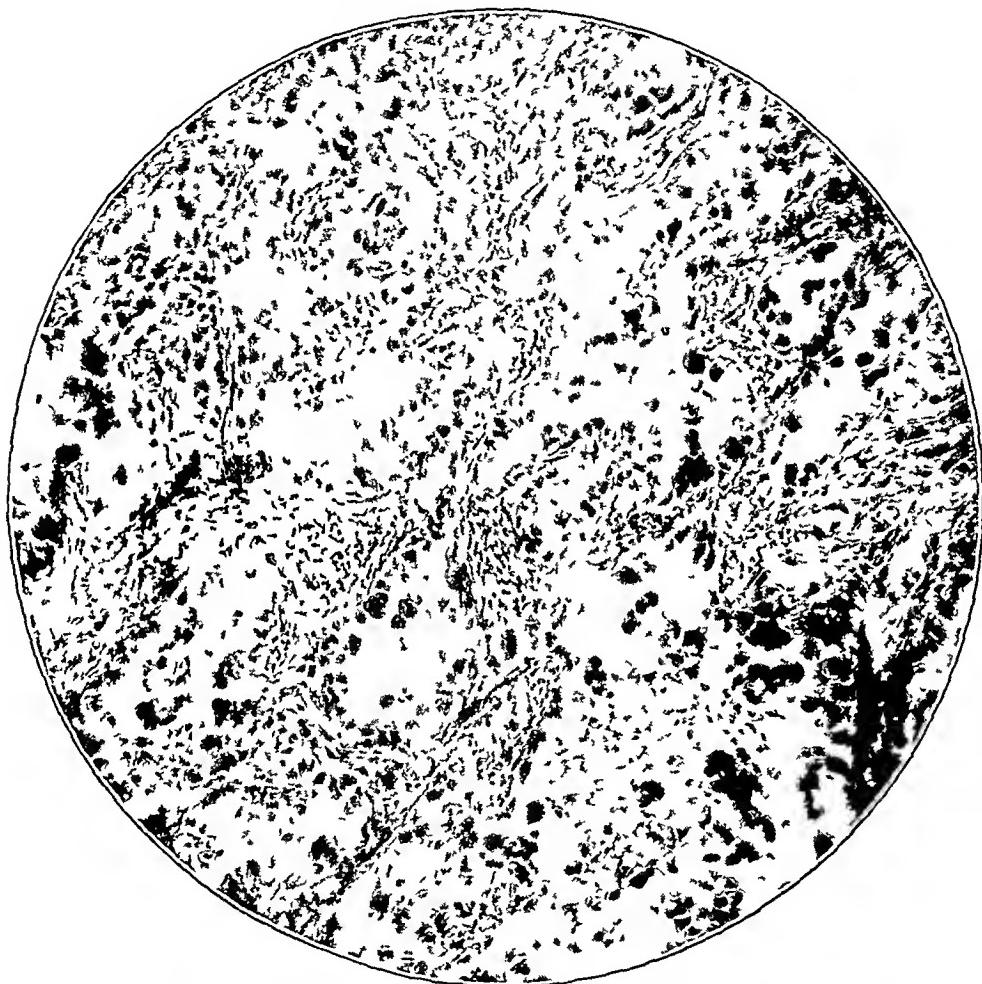


Fig 8 (Case 8).—Primary carcinoma of the lungs, tumor cells replacing the normal alveolar lining, alveoli distended and alveolar walls greatly thickened.

Microscopic Examination.—Lungs. In the right lung, the tumor was made up of epithelial cells which varied in shape from cuboidal to columnar. The cytoplasm of the cells was large and irregular, and their nuclei vesicular, round or somewhat oval, containing from 1 to 2 eccentrically situated nuclei. The tumor was confined exclusively to the alveoli, in which the normal alveolar lining was replaced by tumor cells (Fig 8). The whole lung showed a very marked sclerosis, due to the deposit of fibrous tissue stroma of the epithelial tumor which had invaded the alveoli, leading to marked thickening of the alveolar wall. Due to this process, there was much hemorrhage, and the alveoli contained hemosiderin. Some alveoli were filled with coagulated serum and debris. Cells, singly and in clumps, with a tendency to form alveoli were found. Scattered over the sections, a lymphocytic infiltration was seen with

patches of necrosis. There was an invasion of the pleura by tumor, the cells of which resembled closely those of the lung and arranged themselves in small acini. The pleura was very much thickened and consisted of dense fibrous tissue. In the left lung, the tumor was scattered throughout the whole section, and the tumor nodules varied in size from individual tumor cells to tumor masses, from 1 to 2 mm in diameter. The tumor cells here did not differ from those in the right lung by their tinctorial properties, morphologic character or arrangement. In many areas, tumor had broken into the alveoli, replacing their normal lining and producing some fibrosis. Tumor was found in some small vessels and in general was very conspicuous alongside the vessels, probably in the perivascular lymphatics which were markedly dilated. Mitotic figures were quite frequent. In places free from tumor, except for an emphysematous distortion of some alveoli, the lung proper presented a fairly normal appearance. The pleura on this side also was thickened and invaded by tumor cells, arranged in duct-like manner with distended lumina. The remainder of the pleura consisted of dense, fibrous tissue. The vessels in both lungs were engorged with blood. The bronchi and bronchioles showed the epithelial lining partly desquamated in areas. No inflammatory or hyperplastic changes could be found here.

Rib Here also the tumor had the same alveolar arrangement and the same type of cells. It differed from the growth in the lungs in that the alveoli were in general much larger, somewhat resembling cysts, and the connective tissue stroma was rather abundant.

Liver The main tumor in the liver was made up on the same type of cuboidal or columnar epithelial cells and also was arranged in acini. The other organs did not show any noteworthy microscopic changes.

The pathologic diagnosis was primary carcinoma of the right lung (probably of alveolar origin) with metastases to the left lung, pleura, rib and liver, hemithorax (right), sclerosis of the right lung, chronic fibrous adhesive pleuritis, and passive congestion of the spleen and kidneys.

The histogenesis of the tumor is of interest. It was judged that the tumor originated in the epithelium lining the alveoli, replacing the normal alveoli lining and leading to a sclerosis of the lung with a marked thickening of the alveolar walls (Fig 8). The possibility of such an origin has been much discussed and contested by many authors Ewing,¹ Ménétrier⁴ and the greater majority of pathologists, however, include this type of lung carcinoma in their classification. The tumor is classified as "of alveolar origin" on the gross and microscopic pictures. Microscopically, no signs of new growth could be detected in the larger or smaller bronchi after a long and careful search. The tumor was not confined particularly to the bronchial submucosa—the usual place of origin of mucous gland cancers. Microscopically, the replacement of the alveolar lining by tumor cells was diffuse throughout the entire organ, instead of having occurred in only a few areas, as is seen occasionally in "bronchial origin" tumors (Fig 2, Case 4). The gross appearance of the right lung in this case is of interest and is unusual (Figs 6 and 7). From the clinical point of view, the case is typical, with its gradual onset, course and duration.

CASE 9—History—A. B., a man, aged 64, entered the Peter Bent Brigham Hospital, May 6, 1923, complaining of cough and fever. The family history was not remarkable. Fourteen months before, he had some wheezing and

shortness of breath, lasting for about six months. He entirely recovered from this and was well, until six months before, when he began to have an unproductive but very distressing cough which varied with the weather, being worse during a cool spell and increased by exertion. This had kept up ever since with very little sputum, but, on one occasion, he had hemoptysis. The only pain he had had was substernal and in the epigastrium after paroxysmal coughing. He had lost 10 pounds (4.5 kg) in the last year. The roentgen-ray



Fig 9 (Case 9).—Epidermoid carcinoma of bronchus, posterior aspect of both lungs, trachea and main bronchi, tumor in right (wider) bronchus and right lung.

examination, two months previous to his admission to the hospital, showed a rounded shadow just to the right of the heart shadow, suggestive of a mediastinal tumor.

Physical examination showed dulness over the right lower lobe with increased breath sounds, normal whispered voice and decreased tactile fremitus in this area. The heart was apparently displaced to the right. The temperature was ranging between 99.8 and 103.8 F.

The blood Wassermann reaction was negative. The sputum was mucopurulent and was negative for tubercle bacilli. The stools and the urine were

negative. The hemoglobin was 98 per cent. The red blood cell count was 4,870,000 per cubic millimeter, and the white cell count, 19,000 per cubic millimeter. The differential count was normal. The roentgen-ray examination, on entrance, showed marked clouding of the right base. The heart, trachea and mediastinum were displaced to this side. The "rounded shadow" originally noted was not evident at present, apparently being obscured by the heart shadow.

The patient remained in the hospital twenty-two days, during which time he lost about 10 pounds (4.5 kg.) in weight. Except for signs of a very slight amount of fluid in the right chest, the clinical picture did not change. He was discharged, May 28, unimproved.



Fig. 10 (Case 9)—Epidermoid carcinoma of bronchus, showing tumor nodules covering the exposed heart, N, tumor nodule

The clinical diagnosis was malignant disease of the mediastinum.

June 13, he was readmitted to the hospital. On physical examination, no marked changes were noted. The patient remained in the hospital three days, and was discharged with the diagnosis of carcinoma of the lungs. At home, he developed occasional hemoptysis. The cough and fever continued. He died, April 18, 1924.

The clinical diagnosis was primary carcinoma of the lungs.

Necropsy.—The necropsy was performed by Dr. S. B. Wolbach, fifteen hours post mortem. The body was poorly nourished and did not show any

marks worthy of note. The peritoneal cavity, except for the presence of about 750 cc of clear, yellow fluid, was not remarkable. The pericardial cavity was distended with about 150 cc of a dark red fluid containing flecks of fibrin. The pericardial surfaces, parietal and visceral, were covered with a red, shaggy, adherent, fibrinous material. The heart was normal in size. The striking feature of the organ, in addition to this fibrinous exudate, was the presence of several, from fifteen to sixteen, elevated nodules, from 4 to 12 mm in diameter, which were distributed fairly uniformly over the right and left ventricles (Fig. 6). On incision, they were white, fairly firm and regular,

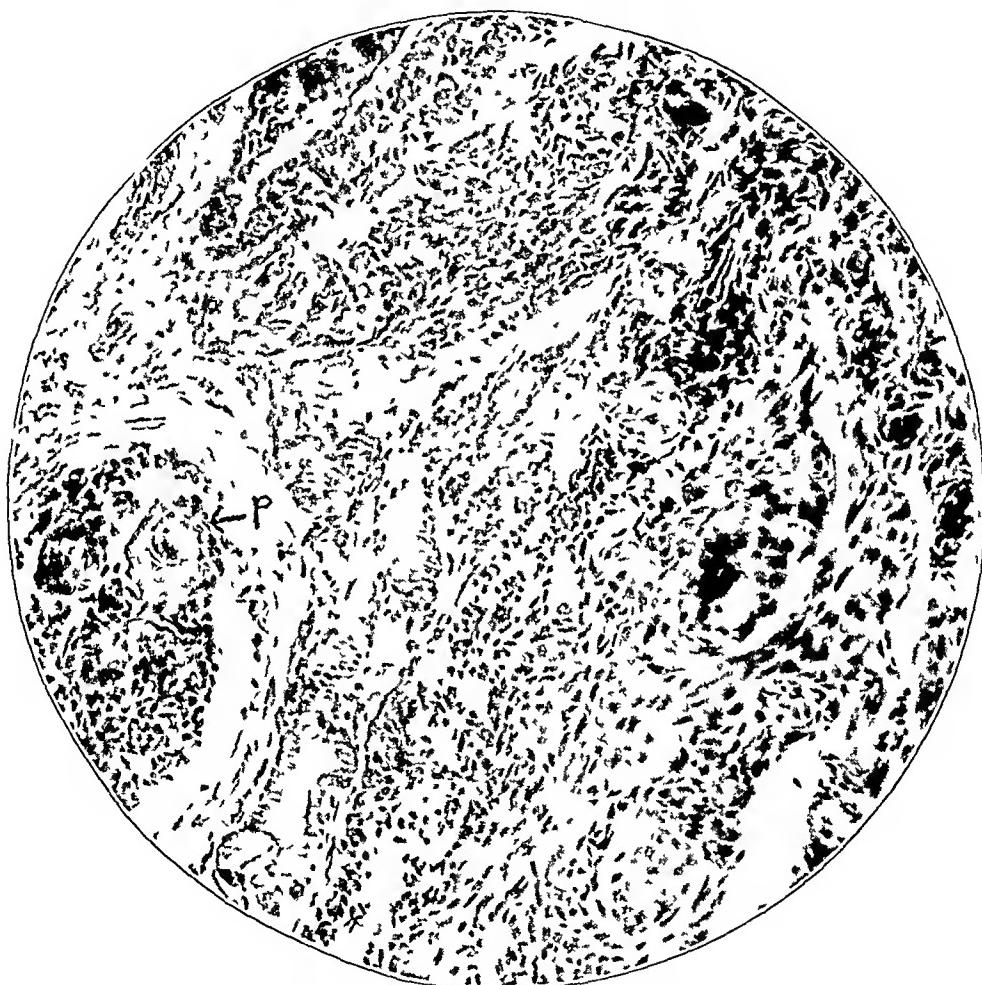


Fig. 11 (Case 9) —Epidermoid carcinoma of bronchus, *P*, pearl formation

and pressure caused to exude droplets of white material, which subsequent microscopic examination showed to be keratinized and necrotic epithelial cells.

Chest The ribs and sternum were adherent on the right side to a thickened pleura along the anterior border of the right lung, and to a hard, firm mass overlying the ascending aorta. The tissues at the anterior mediastinum were edematous. The right pleural cavity was entirely obliterated by very dense tissue. The left cavity was free and contained about 1 liter of clear, deep yellow liquid.

Lungs The right lung was freed by stripping the parietal pleura, and the lungs and heart were removed en masse with the right side of the diaphragm. The pleura over the posterior border of the right lung ranged from 3 mm to 6 mm in thickness, and consisted of dense, white, fibrous tissue with firmer

white plaques, from 2 to 4 mm thick, composed of friable tumor material. There were a few pigmented lymph nodes at the anterior border of the diaphragm which contained numerous white nodules. On opening the trachea and bronchi, the trachea, except for deep injection, was normal. The left primary bronchus also was normal. The right was practically occluded 2 cm below the bifurcation. Anteriorly, the wall of the right primary bronchus was replaced by a friable, white tumor tissue which, on pressure, exuded soft, white material which, on subsequent examination, proved to contain desquamated epithelial cells, the largest part keratinized (Fig 11). The only branch of the right primary bronchus that could be found was one leading to the upper part of the right lobe, and the orifice of this bronchus was nearly completely occluded by tumor tissue. Below, the bronchus ended abruptly in a mass of friable tumor, from 1 to 3 cm in thickness, which extended downward along the inner posterior margin of the lung for a distance of 8 cm. Anteriorly, the tumor, which had replaced the wall of the primary bronchus, extended by direct continuity over the anterior surface of the aorta, forming a layer, 1 cm thick, which extended upward over the ascending portion of the arch. Two parallel incisions were made through the posterior borders of the lungs and showed that the whole lung was atelectatic, with here and there small bronchiectatic cavities. The whole of the upper lobe was tough and fibrous in consistency, and in the peripheral portion of the lung were a few nodules, a few centimeters in diameter, of friable tissue. These tumor nodules were most abundant in the lower lobe. The left lung was not incised. On the inner surface of the lower lobe, that is, in contact with the pericardium, there were two plaques of tumor, each a few millimeters thick and 1 cm in width. The head was not opened. The other organs were normal.

Microscopic Examination.—Lungs. The tumor grew without any definite arrangement. Nests or masses of cells were scattered over the sections surrounded by thick bands of dense fibrous tissue. The tumor cells individually were large, polygonal or elongated and irregular in outline. The cytoplasm was finely granular and stained in blue. The vesicular nucleus occupied the greater part of the cells, was large, rich in chromatin and contained a centrally located, very deeply stained nucleolus. The cells varied slightly in size. Large cells with many nuclei, resembling giant cells, were encountered here and there. In many areas, mostly in the center of the tumor masses, the cells had a tendency to arrange themselves in concentric layers and were conspicuous. Here, the cells were usually larger than the tumor cells, their cytoplasm was stained deep red with eosin, and the nucleus seemed generally to be smaller. These masses of cells had the typical appearance of a cornified epithelium met with in the so-called "pearls" of the epidermoid carcinoma. Here also there was a definite tendency to "pearl" formation (Fig 11). These keratinized masses were sharply demarcated from the rest of the tumor. Wide areas of necrosis were seen in practically all sections. The lung tissue adjacent to the tumor but free from the new growth, showed extensive fibrosis, in areas dense and avascular, in areas rather loose and richly supplied with blood. Large endothelial cells loaded with a brown pigment were disseminated occasionally among the tumor cells and, more conspicuously, in the preserved and compressed or distorted alveoli. Anthracosis and round cell infiltration was seen here and there. The pleura showed invasion by tumor which showed the characteristics of the main tumor. The lymphatics were greatly distended by tumor nodules, which occupied the greater part of their lumen.

Esophagus. The tumor here was confined to the muscularis mucosa and submucosa and was identical to the lung tumor. It was sharply demarcated from the normal tissue. The esophageal mucosa was intact. Mitotic figures in the main tumor, as well as in the metastases, were of a rare occurrence. From the gross appearance and histologic examination, it was judged that the tumor was a slowly growing epidermoid carcinoma originating in the mucosa of the right bronchus. The spleen showed amyloid infiltration. The liver

showed passive congestion and slight central necrosis. The kidneys showed slight arteriosclerotic changes. The other organs were normal.

The pathologic diagnosis was epidermoid carcinoma originating in the right primary bronchus with metastases to the pleura, left lung, heart, regional lymph nodes and esophagus, hydrothorax (left), hemopericardium, ascites, amyloid degeneration of the spleen, and passive congestion of the liver.

It will be noted that the tumor in this case was a slowly growing epidermoid carcinoma originating in the right bronchus. Since the bronchi are normally lined with columnar ciliated cells, the squamous type of cells in this kind of tumor is believed to be due to a conversion of the columnar cells. This conversion or metaplasia is defined as "a transformation of one well characterized tissue into another equally well characterized but morphologically and functionally different." This transformation is, however, limited to epithelial tissues only. The intimate mechanism of this conversion is, as yet, under discussion. It is observed, however, that metaplasia of epithelium is always due to a previous long standing chronic irritation, viz., inflammation. A typical example of such a transformation is seen in leukoplakia of the tongue. Richey¹⁶ reported a case of leukoplakia of the pelvis of the kidney due to a chronic colon bacillus inflammation. Wells¹⁷ described a case of a primary squamous cell carcinoma of the kidney, and considered renal calculi which were present in this case to be the direct cause of the metaplasia which ultimately resulted in malignancy. Wells produced evidence to show that "metaplasia involves not only a morphologic but a chemical transformation of the cells." Haythorn¹⁸ observed metaplasia of bronchial epithelium in three cases of unresolved pneumonia.

The tumor in the case reported grew very slowly, the duration of the disease being about sixteen months.

CASE 10—*History*.—J. E. C., a man, aged 38, a gardener, entered the Peter Bent Brigham Hospital, July 2, 1924, with the complaint of progressive weakness and loss of weight. The past and family histories were negative.

The present illness began, eight months before admission, when he noticed that he was getting unusually weak, and at the same time his friends called attention to the fact that he was getting very thin. Within the following two months, he lost 20 pounds (9 kg), 10 pounds (4.5 kg) of which he has regained in the last six months, by not working, as he said. His appetite became poor about three weeks before. One week before, he began to swell up in front of the left shoulder. For three or four weeks, he had had a cough, coincident with a cold. The cough was present only in the afternoon, and he raised slight quantities of normal looking sputum. He had become so weak that he could hardly sit up in bed. He had been hoarse for one month. He had noticed clubbing of his fingers, the left hand particularly, in the last two weeks.

Physical examination showed a fairly well developed and very poorly nourished cachectic man. There was an edema involving the left shoulder and apex regions. The expansion of the chest was less marked on the left.

16 Richey, D. G. J. Lab. & Clin. Med. 5: 635 (July) 1920.

17 Wells, H. G. Arch. Surg. 15: 356 (Sept.) 1922.

18 Haythorn, J. Med. Res. 21: 593, 1912.

The respiration was 26, and of shallow depth. The thorax was narrow and ptotic. The heart and aorta showed no pathologic condition. The pulse was 110, and was even and regular. The arteries were not remarkable. The veins were dilated in the left arm and neck, and slightly in the right arm. The blood pressure was systolic 85, diastolic 65.

In the lungs the expansion was diminished on the left side. On palpation, no friction rubs were heard. Vocal fremitus was diminished on the left side.

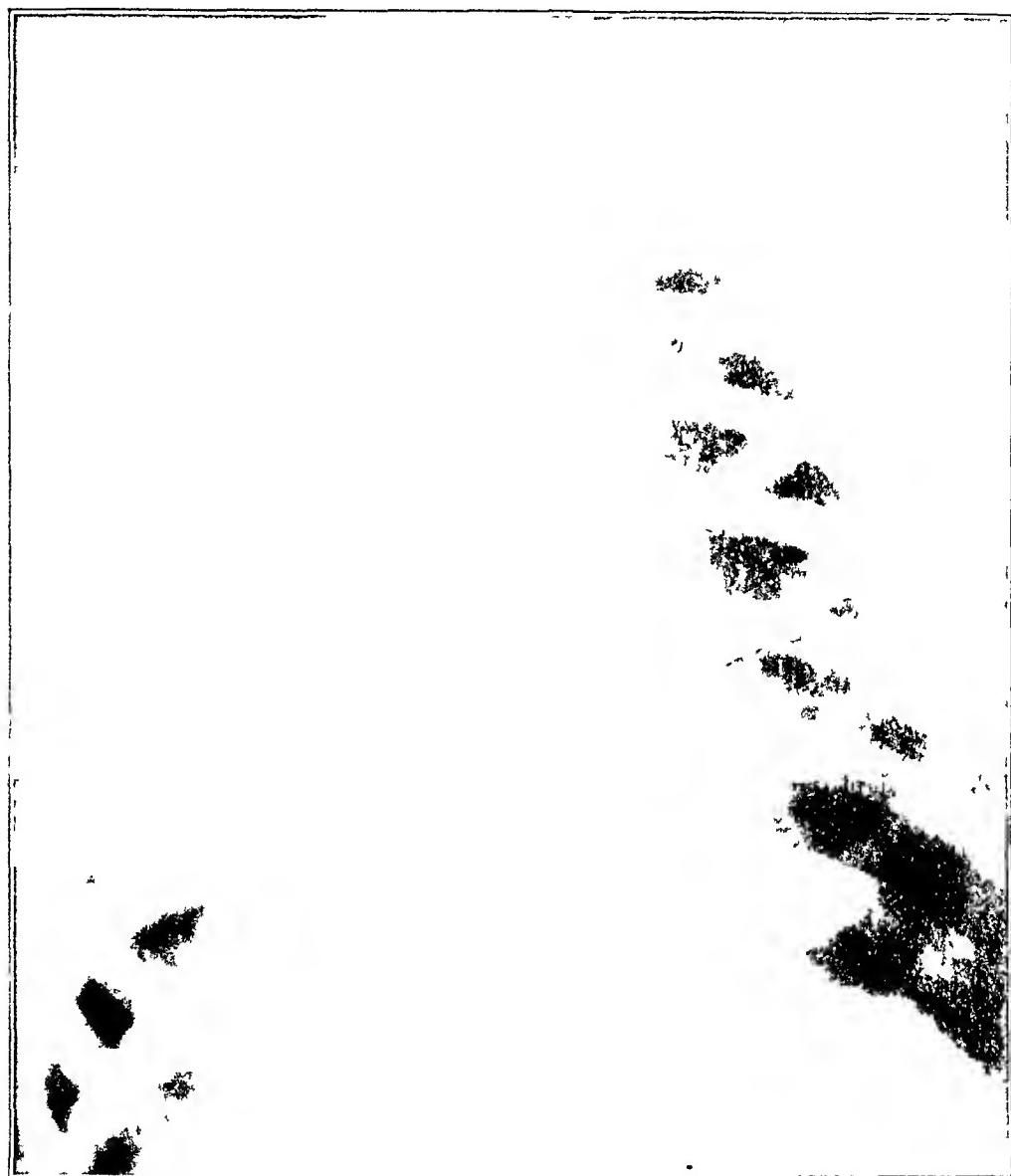


Fig. 12 (Case 10)—Carcinoma of the left lung (Courtesy of Dr. M. Sosman.)

and practically absent posteriorly. On percussion of the left side, the note was flat from the apex to the angle of the scapula, and dull down to the lower border and to the posterior axillary line. Anteriorly, it was dull at the apex, up to the second interspace, below that, normal for an interspace and then markedly tympanic up to the base and along the axillae, as if there were air beneath the pleural cavity. On auscultation, the left side showed posteriorly diminished bronchial breathing at the apex down to the angle of the scapula. Below that, for a stretch of two or three interspaces, the breath

sounds were purely bronchial and close to the ear, at the base, there was distant bronchial breathing. The whispered voice corresponded anteriorly, the breath sounds were bronchial down to the third interspace, and below that to the base, there was distant bronchial breathing. The right side did not show any pathologic condition. The voice did not sound abnormal. The rest of the physical examination, except for the clubbed fingers noted, which were more marked on the left, was not remarkable.

Roentgen-ray examination of the chest, June 10, showed (Fig 12) a large, smooth, dense shadow occupying the upper third of the left lung, extending as low as the eighth rib posteriorly, along the border of the spine and in the third rib in the axillary line. Fluoroscopically, this mass did not pulsate, was not connected with the esophagus, displaced the trachea very slightly and showed no fluid level. The adjacent ribs and spine all appeared normal. The impression of the roentgenologist was that there was a tumor, probably arising in the lung, possibly metastatic.

Reexamination of the chest, July 7, showed a marked generalized haze over the entire left half of the thorax, with a sharp, pleural line along the left axilla, which was characteristic of fluid in the pleural cavity. The heart, aorta and trachea were displaced to the right. Fluoroscopy showed paradox movements of the diaphragms, the left rising and the right falling at inspiration (The latter suggests bronchial obstruction on the left). The definitely outlined shadow previously seen could not be identified.

The blood Wassermann reaction was negative. The leukocytic count was 16,000 per cubic millimeter, the erythrocytes were 2,800,000 per cubic millimeter.

July 5, the patient was tapped, and 1,200 cc of an opalescent fluid was removed, which showed a specific gravity of 1.010 and 100 per cent mononuclear cells.

July 10, a second thoracentesis was attempted. Fluid could not be obtained. On suction, a few small pieces of necrotic material were obtained, and were sent to the pathologic laboratory. The pathologic diagnosis was carcinoma.

Due to a secondary infection, the patient ran a septic fever. He remained in the hospital twenty-two days and died.

The clinical diagnosis was carcinoma of the left lung.

He had had previous hospital entries at Newton Hospital and at Huntington Memorial, Boston, recently. No diagnoses were made there.

Necropsy.—The necropsy, performed by Dr H. Pinkerton and myself, showed a very poorly nourished, cachetic, white man, measuring 170 cm in length. The external examination revealed clubbed fingers, more pronounced on the left, a large decubitus over the sacrum, a slightly prominent abdomen, and a hard, palpable lymph node in the right axilla. Otherwise, the external examination of the body was not remarkable. A primary incision revealed only slight traces of fat over the chest and abdomen. The peritoneal cavity contained 150 cc of clear, straw colored fluid. A membranous exudate about 2 mm in thickness was found overlying the lower portion of the sigmoid colon. Between the hepatic and the splenic flexures, the colon was extremely ptotic, hanging down to the brim of the pelvis. A calcified lymph node 1 cm in diameter was found in the mesentery of the small intestine, containing some cheesy material.

Pleural Cavities.—The right cavity contained about 100 cc of a clear yellowish fluid. The cavity was free throughout. Both the parietal and visceral pleurae were smooth and glistening, and showed no inflammatory changes or invasion by tumor. The left cavity contained about 300 cc of fluid similar to that found on the right side. The cavity was free, except at the apex and posteriorly, particularly along the spine and posterior chest wall where it was obliterated by extremely strong adhesions. The left lung appeared normal in front and in the axillary region from the beginning of the third rib

downward, posteriorly, only the lower lobe was free from tumor. The visceral pleura in the areas untouched by new growth was normally thin and translucent, and the lung was rather pale and slightly emphysematous. The lungs and heart were separated from the pleural cavity en masse.

Owing to strong adhesions, the apical part of the tumor and that part along the spine were torn on removal, a portion being left in the chest. When the visceral pleura was thus torn, it seemed that the tumor walled off by the pleura shelled out from the latter and appeared twice as large as seen *in situ*.



Fig. 13 (Case 10)—Epidermoid carcinoma of left lung, showing anterior aspect of both lungs, tumor is seen above the line.

The tumor was grayish white, moderately firm and somewhat friable. It was composed of one large mass and on the surface in front, a couple of nodules, from 3 to 5 cm in diameter, were seen. The tumor was sharply demarcated from the lung parenchyma.

Trachea and Bronchi. The trachea appeared normal. Its mucosa was pale and covered with a colorless, frothy fluid. The right bronchus and its divisions showed no changes. The main stem of the left bronchus entered as usual the lower lobe of the lung and its dissected ventral and dorsal branches were patent and contained no pathologic condition. The first branch of the left bronchus (normally distributed to the superior lobe) was normal throughout.

Two of its larger intrapulmonary branches, the lower and middle, were patent and appeared normal only for about 3 cm and were occluded at the end by tumor. The other intrapulmonary branches distributed in the superior part of the upper lobe could not be traced at all, being entirely surrounded by tumor and destroyed.

Lymph Nodes The tracheal, tracheobronchial and mediastinal lymph nodes were carefully investigated and did not show any invasion by tumor. The nodes below the bifurcation seemed to be enlarged, without, however, any



Fig 14 (Case 10).—Epidermoid carcinoma of left lung, showing posterior aspect of both lungs, *LB*, left bronchus, *MS*, main stem of left bronchus.

tumor invasion. The third and fourth ribs at the junction of the vertebrae and two thoracic vertebrae were eroded in areas of the tumor attachment, but no invasion of the bone could be demonstrated. The other organs, carefully examined, did not reveal the presence of any new growth or other noteworthy changes.

Microscopic Examination—Lungs Sections taken from different parts of the tumor showed the tumor to be composed of polyhedral cells having a large cytoplasm and a voluminous vesicular nucleus. These were arranged in columns and strands from 2 to 3 cells broad, which anastomosed and branched. In

one section, the cells had a somewhat tubular arrangement, showing their nuclei compressed, pushed toward the periphery and having a rosette-like appearance. In another section, the tumor was rather solid, being arranged in small clumps of cells or short rows of single cells. The cells contained a great variety of inclusions, resembling in areas "parasites" described by some writers, and, occasionally, so-called "bird's eye" inclusions. Round globules of a different size stained in black with methylene blue eosin were conspicuous all over the sections. There was no definite keratinization or pearl formation, but only a tendency to this, particularly in the centers of the larger clumps of cells. A great deal of fat was seen in the cells, as well as between the cells. The stroma of the tumor consisted of a loose, edematous connective tissue infiltrated with small round cells, and here and there with single tumor cells. The tumor was sharply demarcated from the lung parenchyma, which showed compression of the alveoli and thickening of the alveolar wall. Mitotic figures were seen rarely. The lymph nodes showed no signs of tumor. The other organs, except for the kidneys which showed an early parenchymatous nephritis, were not remarkable.

The pathologic diagnosis was epidermoid carcinoma of the left lung of bronchial origin, chronic adhesive fibrous pleuritis, hydrothorax (bilateral), peritonitis, decubitus, clubbed finger, and cachexia.

Nine months before death, the patient began to complain of progressive weakness and of loss of weight. These complaints were the leitmotif of the entire clinical history. The duration of the disease was certainly much longer than nine months, and, as in the previous cases, its real onset was impossible to determine. Of a particular interest in this case was the absence of any complaints referable to chest organs—cough, hoarseness and pain in the chest. It will be seen that the symptoms, loss of weight and weakness, were characteristic of malignancy anywhere in the body. On staff rounds, the visiting physician demonstrating the case said, "It is unusual to have a primary growth in the lungs without cough as the most outstanding feature." By analyzing the cases here reported, one will see that cough was present only in Cases 7 and 9, but was not, however, a prominent feature even in these cases. This case, once more, outlines the "clinical polymorphism," so to speak, of primary lung cancer, and the atypical course it usually runs.

The diagnosis, in this case, was made on a rather incidental "biopsy," due to a suggestion from the pathologic department to insert into the chest a larger needle and to try to aspirate some tumor material for pathologic diagnosis.

The pleural fluid obtained at necropsy and examined by myself after it had been centrifugalized (a smear stained with methylene blue), in addition to small lymphocytes, showed also epithelial cells of an unmistakably malignant nature. It was remarkable that whereas the lymphocytes, in the smears, were always single, the tumor cells were gathered almost always in clumps of five or seven.

Histopathologically, the tumor, as in Case 9, was classified as a slowly growing epidermoid carcinoma originating in a small branch of the left bronchus. It did not metastasize. This is the second case, in the series of ten reported, diagnosed antemortem.

Summary of Cases

Case	Sex*	Age†	First Symptoms	Thinner	Cachexia	Fever	Duration †	Clinical	Pathologic	Type of Tumor
				euthosis	Yes	Yes	Months	Diagnosis	Diagnosis	Bones, liver, supra
1	♂	15	Inability to move right arm, diplopia and pain in left eye	No			5	Carcinoma, origin unknown	Primary carcinoma of lungs, left lower lobe	Lobar type, bronchial origin, emboldal and columnar cells
2	♂	44	Pain in abdomen and chest	No	Yes	No	3	Lymphosarcoma?	Primary carcinoma of lungs, left lower lobe	Lobular type, bronchial origin, columnar cells
3	♀	57	Tumorous pain	No		No	7	No diagnosis made	Primary carcinoma of lungs, left lower lobe	Lobar type, bronchial origin, columnar cells
4	♂	55	Brain symptoms, halberinations, Bell's palsy, projectile vomiting	No		No	5	Alcoholic psychosis?	Primary carcinoma of lungs, left lower lobe	Nodular type, bronchial origin, columnar cells
5	♂	45	Severe headaches and pain in back	No		No	?	No diagnosis made	Primary carcinoma of lungs, left upper lobe	Lobar type, bronchial origin, columnar cells
6	♂	37	Sharp pain in right shoulder and right knee	No	Moderate	No	3	Pulmonary tuberculosi	Pulmonary carcinoma of lungs, right upper and lower lobes	Lobular type, bronchial origin, emboldal, columnar and squamous cells
7	♂	?	Pain in chest and cough	No	Moderate	Yes due to septicemia	7	No diagnosis made	Primary carcinoma of lungs, right upper lobe	Lobular type, bronchial origin, polygonal cells
8	♂	62	Pain in chest and back	No	Yes	No	12	Pulmonary tuberculosi	Pulmonary carcinoma of right lung	Infiltrating type, pleural origin, emboldal and columnar cells
9	♂	64	Cough and fever	No	Yes	Yes	16	Primary carcinoma of the lungs	Fibroendothelial carcinoma of the right bronchus	Infiltrating type, bronchial origin, squamous epithelial cells
10	♂	38	Loss of weight and weakness	No	Yes	Yes, due to peritonitis	9	Carcinoma of left lung	Elderly endometrioma of left lung, left upper lobe	Lobar type, squamous epithelial cells

* In this table, ♂ indicates male, ♀ female

† Since the onset of the first symptoms

COMMENT

1 Metastases—The occurrence of metastases in primary lung carcinoma was reported by many observers. In 374 cases reported by Adler 280 gave metastases. In order of frequency, the regional lymph nodes, liver, pleura and lungs occupy first place, while the brain and bones are very much less frequent.

It will be seen from the accompanying table that in all but four of the cases reported here, there were metastases to the brain and bones. In one instance (Case 1), the tumor involved the medullary portion of the vertebra without producing any changes in the outline of the bone. Such an incidence demonstrates the ease with which bone metastases can be overlooked. In two instances, the brain and the bones were involved, in one, the bones and the fifth nerve, and, in another, the brain and leptomeninges. The invasion of a nerve was reported by Kretchmer and also by Scott and Forman¹⁹ (the tenth). Passlei, quoted by Scott and Forman, described extensions of the tumor into the larger nerves. The appearance of the metastases is apparently early and, as we shall see later, they mask the whole clinical picture.

The analysis of the cases shows that, in Case 1 the first symptoms were directed toward the nerve and bone. In Case 2 the chief complaint was abdominal pain due apparently to the liver metastases, in Case 3, it was lumbar pain, due to invasion of the lumbar vertebrae. In Case 4, the brain symptoms were the sole complaint. In Case 5, the chief complaint was severe headaches and pain in the back, due to brain and bone metastases. In Case 6, pain in the knee was due to metastasis. Case 7 gave metastases only to the regional lymph nodes. In Case 8, in addition to the characteristic pain in the chest, there was a sharp pain in the back (spinal metastases) which occurred about ten months before death.

The importance of such facts is evident in relation to recent progress in intrathoracic surgery.²⁰

2 Clinical Classification—Clinically, primary carcinoma of the lungs is classified in two varieties (Adler, Osler) (1) an acute galloping pleuropulmonic form which runs a very rapid course, from six to twelve weeks, an example of this type of tumor was recently reported by Bergmark and Quensel,²¹ (2) a chronic pleuropulmonary carcinoma which includes the bronchopulmonary type, the mediastinal type and the pleuritic type.

As it was pointed out, the tumor possesses not only a vigorous metastatic power, but its metastasis is very early and most of the symptoms are due to metastatic involvement.

19 Scott, E., and Forman, J. Med Rec 90:452 (Sept 9) 1916

20 Lilienthal, H. Malignant Tumor of the Lung. Necessity for Early Operation, Arch Surg 8:308 (Jan) 1924

21 Bergmark and Quensel, F. Acta med Scandinav 59:710, 1923

Because of this property, the clinical picture may be divided into two groups typical—with the chief complaint concerning the chest organs, and atypical—with symptoms due to metastatic involvement.

The difficulties in the diagnosis of the atypical cases, and they are apparently commonest, are often insurmountable. Only the skill of the clinician and some unexpected "accident" lead to a correct diagnosis in such cases. Ameuille²² reported a case of primary lung cancer recently which gave a typical clinical picture of lung abscess. The roentgen-ray examination was not confirmatory. At operation, pus was found in the thoracic cavity and the French clinician simply, as he says, made a smear from the pus "par curiosité" which, however, revealed that he was dealing with a carcinoma. He labeled his case as a "cancer pulmonaire à forme d' abses". Of twenty-nine cases reported by Cottin, Cramer and Saloz,⁵ a correct diagnosis was made in only 20 per cent. Of eight cases, Cramer and Saloz made a correct diagnosis in six instances, or in 75 per cent. The authors add that the encouraging diminution in error "s'explique dans la plupart des cas par de petits accidents accessoires qui nous ont mis sur la voie du diagnostic".

As regards the typical cases (in our series, Cases 7, 8 and 9) the diagnosis can usually be made. The onset is, as a rule, gradual. On physical examination in early, and not infrequently in advanced, cases, the auscultatory signs are scant and not characteristic. This holds true in primary as well as in secondary lung cancers.

A cough productive of a mucus or mucopurulent sputum intimately mixed or only streaked with blood is one of the earliest complaints that usually lead to a diagnosis of tuberculosis. Hemoptysis, which is not rare at the onset of the disease, strengthens the diagnosis of phthisis.

Pleurisy with a serous, purulent, or, more often, bloody exudate is not infrequent but as is known, it is not pathognomonic of lung malignancy.

A sharp, stabbing pain in the chest, due to an early involvement of the pleura is one of the most characteristic signs of carcinoma of the lungs. There is a complete agreement between the writers on the subject (Wolf, Adler, Cottin, Cramer and Saloz, and Fishberg) that pain in the chest is a very early and constant sign in primary pulmonary cancer. No other disease, and especially tuberculosis, will give such a persistent pain with failure to respond to treatment.

In Cases 7, 8 and 9 here reported, which are apparently more or less typical from the clinical point of view, pain in the chest was the earliest sign and the chief complaint of the patient.

Cachexia is practically always present in cases running a typical course.

²² Ameuille, P. Bull et mem Soc med d hôp de Paris **47** 1312 (July 27) 1923

Fever and night sweats also are occasionally present in lung malignancy.

In cases in which the lesion is confined to the bronchial mucosa or submucosa, respiratory trouble will early point toward a new growth.

The duration of the disease (in typical cases) is practically the same as in carcinoma anywhere in the body. Rapid death (in from two to three months) is reported in some cases. In the cases reported here, the duration (since the onset of the first symptoms) varied from three months to about sixteen months.

Primary carcinoma of the lungs is more than twice as common in men as in women. More than 70 per cent, according to Adler, occurred in men.

The right side is by far the more often affected.

3. Laboratory Examination.—A repeated negative sputum for tubercle bacilli, in the presence of persistent lung symptoms (cough, pain in the chest and blood streaked sputum), especially when in addition there has been a gradually downward course, always suggests malignancy.

Lenhartz²³ found in the sputum of 90 per cent of cases studied by him, large, spherical cells filled with a multitude of fatty granules and associated with an abundance of epithelial cells that were "strangely deformed and possessed clublike or taillike projections." He believes that the fatty granules are pathognomonic of pulmonary carcinoma. Osler²⁴ describes the same cells as a sign of pulmonary cancer, and Adler²⁵ considers them as "strictly pathognomonic of carcinoma of the lungs."

The presence of tumor cells in the sputum has to be accepted with great caution, taking into consideration the abundance of epithelial cells in a normal expectoration. However, repeated morphologic examination of the fresh sputum cannot be overemphasized.

The exudate is, in the majority of cases, bloody. It contains not infrequently tumor cells and the importance of a histologic examination of the effusion is outlined by all writers. Here, the fixation of the material will furnish more constant and reliable results. The fluid is centrifugalized, and the sediment is fixed in 10 per cent formaldehyde or Zenker's fluid and run through paraffin.

Bard,²⁶ by studying the hemorrhagic exudate (pleural, peritoneal) of inflammatory origin and following malignancy, was able to ascertain that, by centrifugalizing the inflammatory exudate (tuberculosis), the supernatant fluid is clear and, on chemical examination (guaiac

23 Lenhartz, XXXVI Congrès de la Soc Allem de Chir, 1907, abstr., Presse mèd 15 229, 1907.

24 Osler The Principles and Practice of Medicine, 1919, p 653.

25 Bard Compt rend Soc de biol 103 170, 1901.

method), contains no traces of blood, while in malignancy (primary and metastatic carcinoma of the lungs, metastatic carcinoma in the peritoneum) the supernatant fluid shows hemolysis. As a result, Bard concluded that the pleural and peritoneal exudate of a cancerous origin possesses a hemolytic action on the patient's red cells, a phenomenon missing in the exudates of infectious origin. Cottin, Cramer and Saloz⁵ attribute "an undeniable value to the hemolytic nature of the cancerous exudate." This, however, is not always true. In tuberculous pleurisy of old standing, the supernatant fluid does not show hemolysis. Some French writers believe that an exudate rich in albumin (about 40 gm per liter) may be considered as pathognomonic of cancer.

4 *Roentgen-Ray Examination*—According to the literature, the roentgenogram in malignancy of the lungs is typical at the onset of the disease. In a study of the roentgenogram in new growths of the lungs, McMahon and Carman²⁶ arrive at the following conclusions:

1 The roentgen-ray examination and the stereoscopic study of the roentgenograms will early point to a pulmonary lesion and its probable nature.

2 The areas of increased density found in primary pulmonary carcinoma are usually quite typical, and can be differentiated from areas of increased density caused by other diseases in the thorax.

In a recent report, Thomas and Farmer²⁷ affirm that, by a roentgenogram, the nature of the new growth may be diagnosed before the appearance of clinical signs.

CONCLUSIONS

Primary carcinoma of the lungs is apparently much more frequent than is commonly believed.

Because of the similarity, from the clinical point of view, of primary lung cancer and a great many chronic lung affections, and particularly chronic pulmonary tuberculosis, primary malignancy of the lungs is often mistaken for phthisis or other lung disease.

Primary carcinoma of the lungs possesses a vigorous metastatic power.

From the cases here reported, it seems that the tumor metastasizes very early, and the bones and brain are apparently much more frequently involved than is generally recognized.

The bones may be infiltrated with tumor without producing any change in the outward structure (Case 1).

26 McMahon, F. B., and Carman, R. D. Am J M Sc **155** 34 (Jan.) 1918

27 Thomas, G. F., and Farmer, H. L. Am J Roentgenol **11** 391 (May) 1924

Because of this property (early metastasis), the chief symptom of the patient, as well as the attention of the clinician, is concerned with the secondary involvement, while the primary lesion is often overlooked.

In any case of chronic lung affection with an atypical course and persistence of symptoms especially if tuberculosis is excluded, malignancy should always be considered. The presence of pulmonary tuberculosis does not exclude the coexistence of malignancy in the same organ.

INTERMITTENT (IMPURE) AURICULAR FLUTTER, WITH SPECIAL REFERENCE TO ONSETS AND OFF- SETS OF PAROXYSMS AND THE EFFECTS OF VAGUS STIMULATION *

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The two cases that are the basis for this report exhibited numerous fleeting paroxysms of abnormal auricular action closely resembling auricular flutter. The mechanisms of these paroxysms, as will be pointed out, may be regarded as forms of slightly "impure" flutter. The remarkable never failing brevity of paroxysms, their rapid and at times almost regular recurrence, furnished striking clinical pictures which, as it seemed to us, deserve emphasis as a clinical entity. Furthermore, these cases are of interest since numerous onsets and offsets of clinical circus movement, of which hitherto there have been but few recorded, were obtained. It has therefore been possible to make certain new observations regarding the onset and offset of clinical circus movement and the effects of vagus stimulation and certain drugs on its incidence and duration.

REPORT OF CASES

CASE 1—J S., a Polish coal miner, aged 50, was admitted to the Medical Division of the University Hospital, June 27, 1923, complaining of cough and palpitation of the heart. Four months previously he had been almost suffocated by dust during an accident in the mines. Since then he had suffered from cough, palpitation of the heart and shortness of breath so that he had been unable to work. His physician informed him that his heart action was irregular. The patient stated that his abdomen had been swollen for two months before admission, but recently had returned to normal size.

The past medical history was negative except for a mild attack of rheumatism lasting for one month, six years prior to admission. The family history was unimportant, and the social history negative except for the fact that he had been a coal miner for twenty-two years.

Physical Examination.—The patient was a robust, well muscled man, younger in appearance than his stated age. There were no visible evidences of distress or discomfort. There was marked pulmonary emphysema. The heart was enlarged, the transverse measurement being 15.5 cm., and there was a blowing systolic murmur at the apex. The ventricular rhythm was irregularly irregular and the rate ranged from about 80 to 100. The arrhythmia was not abolished by mild exercise. There were no evidences of passive congestion.

Routine examinations of the blood and urine, the Wassermann test and chemical studies of the blood all were negative.

Electrocardiograms.—In Figures 1, 2 and 4, are shown the typical disturbances of cardiac mechanism. There were numerous premature auricular beats, a

* From the Medical Division, University Hospital, and the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.

few of which were isolated, but most were followed by short after effects consisting of one or more cycles of abnormal auricular action. In the longer paroxysms there were usually from 6 to 8 cycles. Of these, the first was invariably the longest. A fairly high degree of regularity usually began with either the second or third cycle. In numerous short paroxysms consisting of only three or four cycles, regular action was not established.

Most of the disturbances of rhythm recorded were clearly initiated by premature auricular beats. These occurred apparently haphazard throughout a wide range of auricular diastole. Their effectiveness in initiating after effects did not appear to bear any relation to the degree of prematurity. In a few instances although details of the beginnings of paroxysms were somewhat obscured by ventricular complexes, the evidence appeared to indicate that paroxysms were initiated by auricular beats of sinus origin (footnote).

There were marked differences in rate of auricular beating during paroxysms, manifesting itself in neighboring paroxysms as well as in those more distant from each other. The lengths of initial cycles (from peak of first

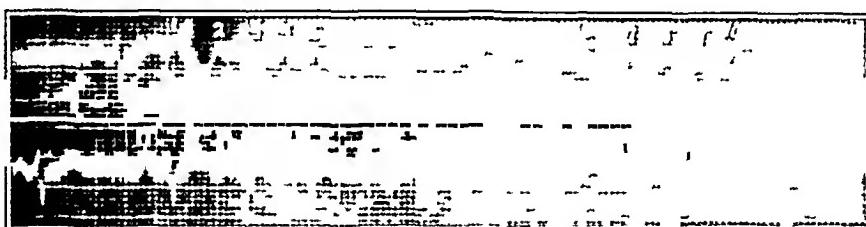


Fig 1 (Case 1)—Continuous tracing, Lead II. Four short paroxysms, all initiated by premature beats in various stages of auricular diastole. One offset (:) is recorded during ventricular diastole.

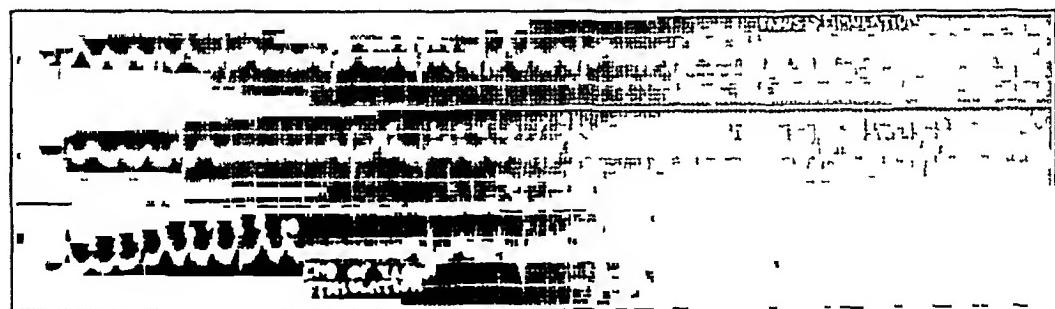


Fig 2 (Case 1)—Continuous tracing, Lead II, showing effect of vagus stimulation (pressure over both carotid sheaths). The paroxysm from 1 to 10 is longer than any obtained except under vagus stimulation. The cycle n to o exhibits the exaggerated slowing of rate just preceding offset, sometimes found during vagus stimulation.

deflection to peak of second) varied at least 0.09 second, the extreme measurements being 0.23 and 0.32 second. After regularity was established, the rate of beating ranged approximately from 270 to 360 per minute.

The offsets were usually preceded by the lengthening of the last one and occasionally the last two cycles. In a few paroxysms, offset was abrupt, not being preceded by slowing. After offsets, the duration of periods of auricular inactivity before resumption of normal beating was somewhat variable. Usually, but not always, they exceeded slightly the following cycles of sinus rhythm (postundulatory pause).

The ventricular rhythm was made highly irregular by the auricular action. The initial premature auricular beats were usually followed by ventricular

contractions, but thereafter ventricular response was irregular, occurring after two, three or four of the abnormal rapid auricular beats. Isolated premature contractions and postundulatory pauses also contributed to the irregularity.

Vagus Stimulation—Results of vagus stimulation are seen in Figures 2 and 3. No influence in the direction of inhibiting onset of flutter was observed after ocular pressure or pressure over one or both vagi. There was a distinct tendency toward slight prolongation of paroxysms during the various types of vagus stimulation. There was also, in some instances, exaggeration of the slowing of auricular beating just preceding offset. One decidedly prolonged paroxysm was recorded in which there was alternate waxing and waning of the auricular rate (Fig. 3, strip 2).

Exercise—Observations on the effect of exercise were unsatisfactory because the patient did not cooperate well. Mild exercises such as walking up and down stairs rapidly had no manifest effect on the arrhythmia.



Fig. 3 (Case 1)—Upper strip, Lead II, beginning of a period of ocular pressure. Prolonged paroxysm, with marked exaggeration of slowing preceding offset (9, 10, 11, 12). Lower strip, Lead II, end of a period of ocular pressure. The final portion of a prolonged paroxysm shows definite waxing and waning of rate with marked slowing at 9, 10, 11 and 20, 21, 22, 23.

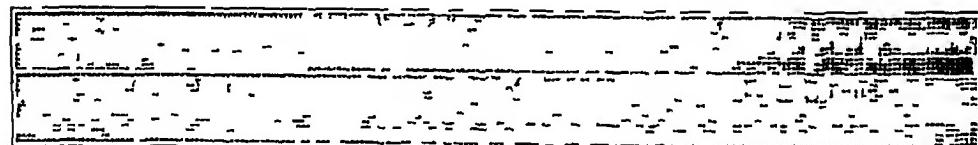


Fig. 4 (Case 1)—Upper strip, Lead II, made just before administration of atropin; lower strip, Lead II, thirty minutes after hypodermic injection of 4 mg of atropin sulphate. In places (1), premature auricular beats appear to bear a constant relationship to preceding beats of sinus origin, suggesting that the premature beats are "re-entrant" and that paroxysms following these events are really initiated by sinus beats. A comparison of initial cycle lengths in second and third paroxysms, lower strip, supports this view.

Atropin—The effects of hypodermic injection of 2 and 4 mg of atropin were observed. In both instances, the results were identical. Auriculoventricular conduction during paroxysms was improved so that the rhythm was predominantly two to one (Fig. 4). The incidence of paroxysms was slightly increased. No definite influence was noted in respect of the lengths of paroxysms nor the rates of beating during paroxysms.

Quinidin—Quinidin sulphate in small doses had no effect on the arrhythmia, but 0.6 gm three times a day almost completely suppressed it. The cardiac action became entirely regular except for isolated premature auricular beats and occasional abortive after effects consisting of only one or two beats. Quinidin was not well tolerated by the patient and he complained of vertigo and extreme weakness. After discontinuance of the treatment, the characteristic arrhythmia returned within forty-eight hours.

Digitalis—During the first trial of digitalis, the heart action became entirely regular after digitoxin in dosage of 0.1 gm three times a day had been received.

for three days. On subsequent trial of the drug, the arrhythmia was again abolished except for occasional isolated premature auricular contractions. Daily small doses of digitalis were continued for ten days and the flutter did not reappear. The patient then left the hospital, stating that he felt greatly improved.

CASE 2.—Mrs T., aged 48, a patient of Drs Joseph Sailer and Charles H. Frazier, was admitted to Dr Frazier's service in the University Hospital, Dec 19, 1923, to be operated on for hyperthyroidism. The heart action was rapid and highly irregular, and could not be differentiated clinically from auricular fibrillation. An electrocardiogram showed numerous premature auricular beats and a few short paroxysms of very rapid auricular action (Fig 5) which resembled somewhat the paroxysms recorded in Case 1. None

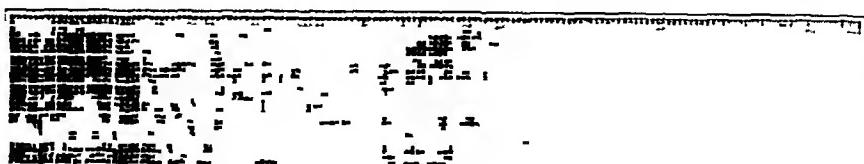


Fig 5 (Case 2)—Typical brief paroxysms, initiated by premature auricular beats, and showing continuous acceleration up to the abrupt offsets

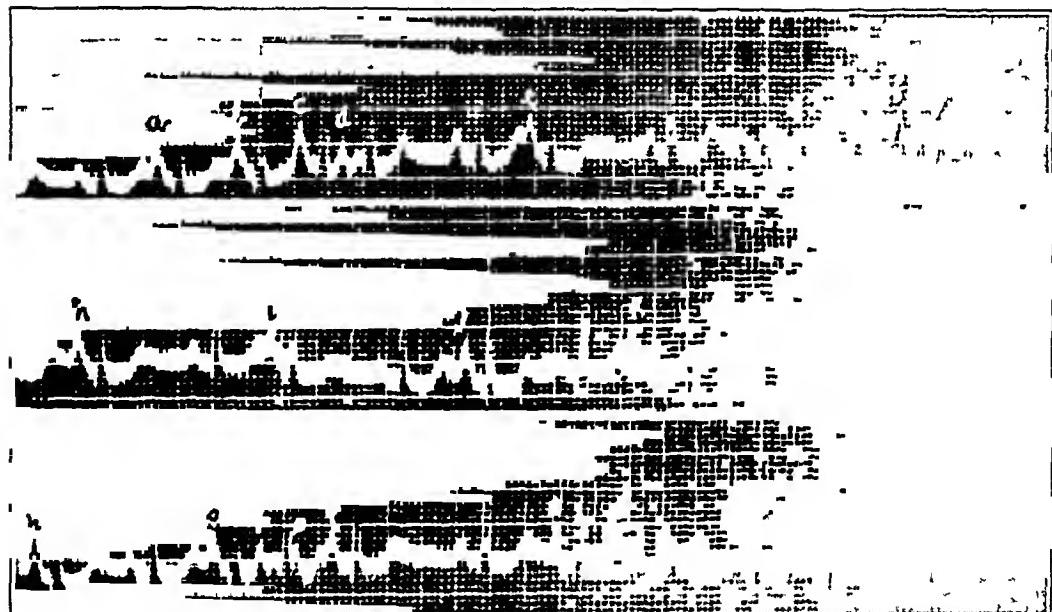


Fig 6 (Case 2)—Continuous strip, Lead II. Frequent isolated premature auricular contractions. Succession of three premature contractions (*k*, *l*, *m*). Note similarity of deflections, *c*, *d*, occurring after two successive premature beats, to *f*, *g*, which are isolated, and to *o*, *p* which initiate a very brief paroxysm

of the paroxysms contained more than five cycles. All were initiated by premature auricular beats of the same form as the isolated premature beats. A regular rate of beating was not established. There was continuous acceleration from cycle to cycle up to point of offset. The cycle intervals of one paroxysm, as measured without special apparatus, were 0.27, 0.20, 0.16 and 0.14 second respectively. The offsets were abrupt.

Following the administration of digitalis, the cardiac rate diminished, the arrhythmia decreased but did not entirely disappear. Bipolar ligation of the

thyroid arteries, one week after admission, was well borne, but the cardiac rate again greatly accelerated and the arrhythmia increased so that it once more simulated auricular fibrillation. A tracing made ten days after operation (Fig. 6) showed isolated premature auricular contractions, successions of premature contractions and short paroxysms of rapid auricular beating similar to those found before operation.

The results of operation were excellent and the patient left the hospital greatly improved. The disturbances of rhythm were greatly diminished and in the course of several months disappeared entirely. The patient was readmitted to the hospital May 10, 1924, and partial thyroidectomy performed May 16. Before operation the heart action was perfectly regular. During the first two days after operation there were numerous premature contractions, and on the third day an arrhythmia that clinically seemed identical with that noted on previous admission. No tracing was made. By the fifth day, the action was regular and has remained so since.

COMMENT

Literature—Tracings of very brief paroxysms of flutter, onsets and offsets of paroxysms are exceedingly rare. Ritchie¹ in 1912 described and published tracings of an arrhythmia that he designated "an intermittent form of auricular flutter." In Ritchie's case, the arrhythmia continued for a number of weeks. The curves showed short paroxysms of rapid auricular beating separated from each other by periods of auricular inactivity of about 0.7 second duration. There was no normal type of beating separating paroxysms as in our cases. Ritchie states that the auricular deflections during paroxysms were similar to those obtained when the heart was beating normally. In view of this statement, it would appear to be difficult to rule out paroxysmal tachycardia arising in the sinus node or its neighborhood as a possible interpretation of the curves.

Semerau,² in 1918, published, along with some tracings exhibiting short paroxysms of auricular fibrillation, one tracing in which a very brief paroxysm was interpreted as auricular flutter. The curves showed some irregularities in the rhythm and the shape of the deflections.

Straus and Hamburger,³ in a recent report in which the relations between gallbladder disease and cardiac arrhythmias were discussed, published tracings of one case in which short paroxysms of flutter are recorded.

Nomenclature—According to present day nomenclature, pure auricular flutter is understood to be a condition in which there is established a continuous, rapid, highly regular circulation of the crest of the excitation wave through a fixed path in auricular muscle, and in addition, an orderly spread of the centrifugal waves throughout the auricles. In

1 Ritchie, W. T. Auricular Flutter, Edinburgh M. J. 9 485, 1912.

2 Semerau, M. Ueber Ruckbildung der Arythmia Perpetua, Deutsch Arch f klin Med 126 161 (May) 1918.

3 Straus, D. C., and Hamburger, W. W. The Significance of Cardiac Irregularities in Reference to the Operability of Cases of Cholelithiasis, Cholecystitis and Duodenal Ulcer, J. A. M. A. 82 706 (March 1) 1924.

neither of our cases did any of the paroxysms recorded conform strictly to such a standard. They were more comparable to the short "after effects" so frequently observed in dogs following a high rate of stimulation of auricular muscle.

We have naturally hesitated to class these very fleeting disturbances of auricular mechanism observed in our cases under auricular flutter, yet it seemed proper to do so. In Case 1, the auricular deflections were strikingly similar in shape, and irregularity was associated only with onsets and offsets. When the paroxysms lasted long enough, regularity was established. In Case 2, obviously, pure flutter did not occur, yet the similarity in details of the paroxysms to each other (particularly in respect of the shape of the auricular deflections and the progressive acceleration of beating) shows clearly that these disturbances have far more in common with auricular flutter than with auricular fibrillation.

Lewis⁴ has described and discussed in detail various conditions found experimentally, which he calls "impure flutter." The disturbances may be very slight and limited to so small a portion of the spread of the centrifugal waves throughout the auricular muscle that they may even escape detection in the axial electrocardiogram. On the other hand they may be profound and interfere markedly with the orderly course of the central or mother wave. Various gradations between pure flutter and fibrillation have been recorded. Garrey⁵ states that impure flutter is essentially the same as pure flutter and should be treated as such, yet it seems to us that the distinctions made by Lewis deserve emphasis, since they afford a basis for a clearer understanding of the mechanisms underlying these conditions. Our cases, as judged from the electrocardiograms, may therefore be regarded as exhibiting impure flutter, not so very far removed from pure flutter, although, as we shall point out, there are doubtless disturbances in the central paths of the excitation waves.

We have borrowed Ritchie's term "intermittent auricular flutter" to direct attention to the intermittent distribution of the paroxysms (particularly well manifested in Case 1).

Onsets.—Lewis, Drury and Bulger⁶ state that in the experimental production of flutter "the circus movement which underlies flutter is provoked when an effective shock enters auricular muscle while the latter is in a critical condition. The critical condition is the condition of partial refractoriness brought about by a high rate of beating."

4 Lewis, T. Observations upon Flutter and Fibrillation, Part IV Impure Flutter, Theory of Circus Movement, Heart 7 191 (Aug 27) 1920

5 Garrey, W E. Auricular Fibrillation, Physiol Rev 4 215 (April) 1924

6 Lewis, T., Drury, A N, and Bulger, H A. Observations upon Flutter and Fibrillation Part IV The Refractory Period and the Rate of Propagation in the Auricle Their Relation to Block in the Auricular Walls and to Auricular Flutter, etc., Heart 8 141 (May) 1921

Lewis admits, however, that he is not prepared to explain flutter following a single stimulus or breaking in spontaneously on a slow heart rhythm.

De Boer⁷ found that single stimuli applied to a frog ventricle some time after recovery from the refractory period caused extrasystole, whereas a stimulus applied immediately after the refractory phase caused a continuous circulation throughout the ventricle. He believed that the weak contraction was followed by a short refractory phase which permitted the circulation of the wave to become established. This hypothesis assumes the temporary presence of localized block (barriers of refractory tissue) in the muscle, initially barring the passage of the wave in certain directions.

Garrey,⁵ to whose fundamental work on this subject we owe so much, states that the normal impulse from the sinus region or any other impulse may cause fibrillation and the wildest incoordination of shuttling impulses, if only the musculature is in what may provisionally be called the fibrillary state.

When we come to examine the hitherto scanty clinical evidence bearing on the manner of origin of the circus movement, we find that nearly all the onsets of flutter and fibrillation recorded have taken their origin from ectopic auricular beats. An exception appears to be found in a case published by Semerau,² in which curves indicate that two onsets of auricular fibrillation originated from sinus beats.

Our cases show definitely the importance ectopic impulses may assume in the production of clinical circus movement, since out of many hundreds of paroxysms recorded, all in Case 2 and the great majority in Case 1 were clearly initiated by premature ectopic auricular beats.⁸ In view of the fact that ectopic beats in our Case 1 falling late in diastole were quite as effective in initiating circus movement as those occurring early, the hypotheses of Lewis and De Boer, which were not meant to apply beyond the experimental conditions presented, cannot

7 De Boer, S. Eine neue Theorie ueber das Entstehen von Kammerwuhlen, Arch f d ges Physiol 178 1, 1920.

8 There is some evidence suggesting that in a few instances among the tracings made in Case 1, auricular beats of sinus origin played some part in the initiation of paroxysms. At times, isolated, highly premature auricular beats occurred simultaneously with T-waves. Their relations to preceding P-waves could not be measured accurately, but in view of their superimposition on T-waves, were undoubtedly fairly constant, suggesting that "coupling" was present. Occasionally this appearance of coupling was followed by a short run of flutter (Fig 4, upper strip). Under such circumstances, the cycle length from peak of premature beat to peak of next deflection did not show the prolongation present in the first cycles of other paroxysms. The time intervals between the coupled beats did correspond roughly to the time of prolonged initial cycles in other paroxysms. It may be that the highly premature beats were "re-entrant" and their mechanism of the nature of circus movement. Under such circumstances, it might properly be held that paroxysms following these events were initiated by sinus beats.

be valid for Case 1, unless it is assumed that a condition of partial refractoriness of human auricular muscle may persist as long as one second (since during periods of slow rhythm, some of the ectopic beats initiating flutter were approximately that far removed from the preceding sinus beat). Such long periods are apparently possible in the case of junctional tissues, but as to whether or not they may occur in auricular muscle, we have no information. In the present state of our knowledge we cannot go beyond the statement that some localized block must occur in auricular muscle, preventing the orderly spread of the impulse and thus preserving tissue to become receptive to the wave after it has encircled the chamber traveling in the opposite direction.

The close clinical relationship among premature auricular beats, paroxysmal auricular tachycardia, auricular flutter and auricular fibrillation has long been observed and commented on. The tracings of our Case 2 we believe, demonstrate particularly well the close relationship among the first three. We find, in a relatively short strip of tracing (Fig. 6), isolated premature beats, successions of premature beats resembling the onsets of paroxysmal tachycardia, a short run of flutter initiated by a premature beat, and two deflections resembling the onset of flutter following two successive premature beats.

It is of interest to note the significance of premature auricular contractions in relation to the circus movement. Our cases show clearly that these may be portals of entry for the circus movement. It is doubtless possible as observations of Garrey and of Semeau indicate, and as is suggested by some of our curves, that the circus movement may take its origin from a sinus beat. Nevertheless, the statement appears to be justified that if auricular muscle is in a state receptive of the circus movement, premature ectopic auricular contractions favor the entrance of the circus movement far more readily than normal type of auricular beats.

Acceleration of Rate Following Onsets of Paroxysms—An acceleration of rate was found in the beginnings of paroxysms similar to that found by Lewis, Feil and Stroud⁹ in experimentally produced short after effects and flutter. These authors explain this phenomenon as being due to the straining of conduction during the period the stimulation just preceding the circus movement. Consequently the first circus movement of the after effect takes place comparatively slowly, this first slow circuit inducing some recovery of conduction so that the succeeding circuits are accomplished more quickly. In our cases, there is naturally no period of stimulation preceding the circus movement which may be invoked to account for a strain on conduction. If we accept the view

⁹ Lewis, T., Feil, H. S., and Stroud, W. D. Observations upon Flutter and Fibrillation Part III Some Effects of Rhythmic Stimulation of the Auricle, Heart 7 247 (Aug.) 1920.

that conduction is initially retarded, we are unable to relate it to preceding events but must regard it as due to a pathologic state of the muscle.

While we are in no position to deny that change in rate of propagation of the impulse, due either to change in rate of fiber conduction or in the duration of the refractory phase of auricular muscle, may play a part in the acceleration of rate observed in our cases, yet it seems to us that there is another factor to be taken into account that may be of importance. It is unlikely that the foci, from which the initial ectopic impulses spring, lie directly in the path which will be assumed by the crest of the wave after circus movement is established. Consequently, acceleration might be due merely to shortening of the central path during the first few beats, irrespective of any changes in conduction or refractory period.

Offsets.—In view of the fact that in both of our cases the circus movement could not be maintained for more than a few beats (in contrast to nearly all cases of clinical auricular flutter hitherto described), it is of interest to examine the curves of offset. There was one distinct difference between the two cases in the behavior of the circus movement just preceding offset. In Case 1, offset was either abrupt without preliminary disturbance in rate, or more commonly was preceded by distinct slowing for one or two cycles. In Case 2, there was continuous acceleration up to point of abrupt offset. It would therefore appear that the factors concerned in the termination of the arrhythmia were not identical in the two cases.

In the present stage of our knowledge, it must be recognized that attempts to explain the mechanism of offset of clinical flutter from electrocardiograms must be purely speculative. We have no information as to the rate of fiber conduction, the duration of the refractory phase, the position of the central path or possible changes in the central path of the excitation wave. It should be pointed out, however, that in very brief paroxysms, as opposed to established flutter, it is not necessary to assume changes either in the rate of fiber conduction or duration of the refractory period to account for the termination of the circus movement.

In Case 2, the closure of the gap and the termination of the circus movement may have been brought about by the election of a progressively shorter central path. This hypothesis would account not only for the continuous acceleration of beating but also the brevity of paroxysms. The events may have been modified by lack of balance between rate of propagation of the wave and recovery from the refractory phase, so that possibly two mechanisms were operating to close the gap.

For Case 1, the simple hypothesis of mechanism of offset we have suggested as applicable to Case 2 is not valid. In the longer paroxysms,

regular rate of beating was established, indicating that the excitation wave was traveling in an established circuit at a regular rate. Here the failure of the circus movement to persist is susceptible of two interpretations.

1 It may be assumed that a condition of stability is not attained because the rate of propagation of the wave allows for complete circulation in the fixed path at a rate slightly in excess of the time necessary for recovery from the refractory phase. Under such circumstances, a gap at first entirely adequate for the perpetuation of the circus movement would gradually narrow and eventually close. The closure might be abrupt or might be preceded by slight slowing as the crest of the wave encountered barriers of refractory tissue, or was forced into a longer path.

2 The second hypothesis involves the assumption of a prolongation of the refractory period of auricular muscle shortly after the establishment of the circus movement. According to Lewis,¹⁰ prolongation of the refractory period is the mechanism responsible for the termination of the circus movement after the administration of quinidin. In the type of cases considered by Lewis, however, the circus movement was of comparatively long duration and thus conditions were not the same as in our Case 1. It is necessary in a regular circus movement of more than momentary duration that the central path must follow a course of the proper length to establish equilibrium between the rate of conduction and the rate of recovery from the refractory phase. Under such circumstances, to change the central path of the circus movement or to terminate it, there must of necessity be a disturbance of the balance between duration of refractory phase and the rate of fiber conduction.

We are unable to deny that prolongation of refractory phase following the onset of flutter may have occurred in our Case 1 and may have been solely responsible for the termination of the flutter. We have practically no knowledge of what influence pathologic changes in auricular muscle may exert on the refractory period. We wish to emphasize, however, that it is not necessary to attribute the termination of very brief circus movement to such a mechanism and regard failure to establish equilibrium between rate of propagation of the wave and refractory period as a far more likely explanation of the early termination of the circus movement.

Vagus Stimulation.—The conspicuous effects of vagus stimulation in our Case 1, namely, general tendency toward prolongation of paroxysms and increased slowing of auricular rate just preceding offset, are manifestations of vagus action not hitherto described in clinical

¹⁰ Lewis, T. The Actions of Atropin and Quinidin in Fibrillation of the Auricles, Clinical and Experimental Studies, Am J Med Sc **164** 1 (July) 1922.

flutter Vagus stimulation was studied by Wilson¹¹ in a case of paroxysmal flutter lasting for several days In his case, distinct acceleration of auricular rate was obtained

Lewis, Drury and Bulger¹² have found that vagus stimulation in dogs conspicuously reduces the refractory period of the auricle but has no direct effect on fiber conduction Quickening of rate has been explained by them as due to removal of partial barriers of refractory muscle in the path of the advancing wave which had compelled it to assume a sinuous course Acceleration of rate under such circumstances is not due to increased rate of fiber conduction, and it need not be due to the assumption of a new central circus path Wilson favored the view that the acceleration observed in his case was due to the assumption of a shorter central circus path, this having been made possible by widening of the gap through reduction of the refractory period Here, again, reduction of the refractory period is regarded as of fundamental importance

The results of Lewis, Wilson and others who have observed acceleration, or even auricular fibrillation and rapid reexcitation of the auricles under vagus stimulation, are not necessarily contradictory to ours, since the former were obtained in established experimental or clinical flutter Our results may also be explained on the basis of a reduced refractory period If the mechanism we have proposed in explanation of the brief paroxysms in Case 1 is correct, namely, that in the circus path established, flutter is not maintained because rate of conduction is in excess of rate of recovery from the refractory phase, it is to be expected that reduction in refractory period would tend toward equalization of these functions and thus have a tendency to prolong paroxysms Under such circumstances also, the gap would tend to close more gradually Thus the period during which the advancing wave traveled through partially refractory tissue might be prolonged and the rate of circus movement just prior to its termination, be more retarded The clinical findings are in accord with these considerations

If we accept the alternative hypothesis to account for the very brief paroxysms, namely, that they are terminated by more or less abrupt depression of the refractory period, the lengthening and more gradual offset under vagus stimulation must be regarded as due to a postponement of the depression of refractory period and to more gradual depression There are, so far as we know, no experimental or clinical

¹¹ Wilson, F N Report of a Case of Auricular Flutter in Which Vagus Stimulation Was Followed by an Increase in the Rate of the Circus Rhythm, Heart 11 61 (Jan 30) 1924

¹² Lewis, T , Drury, A N, and Bulger, H A Observations upon Flutter and Fibrillation Part VII The Effects of Vagal Stimulation, Heart 8 141 (May) 1921

precedents for such an action of the vagus on the refractory period, but the possibility of its occurrence cannot, at present, be denied.

The markedly prolonged paroxysm with waxing and waning of auricular rate (of which a part is shown in Figure 3, lower strip) was the most striking effect produced by vagus stimulation. The periods of slowing resemble closely the tracings of offset under vagus stimulation up to the point that acceleration begins again (compare upper and lower strips, Figure 3). Now unless it may be assumed that in diseased auricular tissue fiber conduction may be retarded by vagus stimulation (of which there is apparently no evidence) slowing must be due to narrowing of the gap between the crest and wake of the excitation wave causing the crest to take up a more sinuous course over the same general path or else seek a new longer circuit. With such a slow circulation of the wave as was recorded, it is apparent that if the wave is permitted to continue, the gap must speedily widen since the rate of circulation is now so prolonged as to give ample time for recovery from the refractory phase. Under such circumstances acceleration of rate of beating is brought about either by removal of barriers of refractory muscle (if we assume that slowing had been due to more sinuous course of the wave over the same general path) or by re-entrance on a shorter path (if we assume that slowing had been due to assumption of a longer path).

We conclude, therefore, that the effects observed from vagus stimulation are due to reduction of the refractory period of auricular muscle. Slight reduction results in slight prolongation of paroxysms. More marked reduction results in comparatively prolonged paroxysms with waxing and waning of auricular rate. Had even greater reduction been possible it is entirely probable that equilibrium between rate of propagation of the wave and duration of the refractory period might have been established (for the period of stimulation) and pure flutter obtained. The nearest approach to pure flutter produced by vagus stimulation was twenty cycles of regular beating.

Atropin.—It was anticipated that atropin in full physiologic dosage might exert a favorable effect on the arrhythmia, either by eliminating premature auricular beats, as it frequently does in the case of ordinary premature auricular contractions, or by shortening the periods of circus movement. The latter expectation was aroused particularly on account of the fact that vagus stimulation had been shown to prolong paroxysms. Although it has been known for a long time that atropin is capable of provoking auricular fibrillation in some experimental animals, Lewis¹⁰ is authority for the statement that atropin is usually an effective remedy for fibrillation in dogs, and suggests that while it is not effective clinically in chronic cases of fibrillation, it might be so in more acute cases. In order to test the value of this interesting suggestion in the type of

case dealt with here, we studied the effects of both 2 and 4 mg of atropin injected hypodermically, with practically negative results, so far as auricular arrhythmia was concerned. In this connection, however, it should be pointed out that vagal tone was probably not very great in this patient, since in spite of dilatation of pupils, impaired vision, flushing, dryness of the mouth, difficulty in swallowing and garrulity, the rate of sinus beating was not increased more than 18 per minute by atropin.

Quinidin.—The remarkable effects of quinidin both in suppressing premature contractions and terminating circus movement are familiar to all who have had experience in the use of this drug. Both effects were conspicuously exhibited in Case 1. It is of interest that the favorable action was not prolonged for more than forty-eight hours after withdrawing the drug. Such a result is what might have been anticipated in view of the rapid excretion of quinidin.

Digitalis.—We have occasionally observed either partial or complete suppression of premature auricular beats under the influence of digitalis, such as resulted in Case 1, but the inhibition of circus movement was unexpected. The complex action of digitalis on the auricle, due to the fact that its direct effect on auricular muscle and its indirect effect produced through the vagus nerve are opposed to each other, makes speculation as to the mode of its action in our case profitless. Of practical importance is the fact that of the various methods of treatment attempted, digitalis produced by far the most beneficial results. In the first case, it abolished the arrhythmia except for occasional premature beats, in the second case, it definitely lessened the arrhythmia. In both cases its use was attended by distinct subjective improvement.

SUMMARY

1 Two cases are reported, both exhibiting numerous fleeting paroxysms of slightly impure auricular flutter. This form of arrhythmia, not hitherto described, deserves rank as a clinical entity and should have reserved for it the name intermittent auricular flutter which was first applied by Ritchie to a somewhat different condition.

2 Numerous tracings of onsets of paroxysms were recorded and the variations among them pointed out. The significance of premature ectopic auricular beats in the initiation of circus movement is discussed.

3 Differences in tracing of offsets in the two cases are demonstrated, indicating differences in mechanism of offsets. An attempt has been made to account for the phenomena bringing about offsets in the two cases.

4 The effects of vagus stimulation were studied in Case 1. The most conspicuous effects were prolongation of paroxysms and exaggeration of slowing of auricular rate just preceding offset. On one

occasion there was found not only prolongation of a paroxysm but alternating periods of rapid and less rapid auricular rate. These phenomena are regarded as due primarily to reduction of refractory period of auricular muscle by vagus stimulation.

5 Atropin in full physiologic dosage exerted no significant effect on the arrhythmia in Case 1 except to improve auriculoventricular conduction. Quinidin and digitalis were both effective in suppressing the arrhythmia.

6 Digitalis in moderate dosage decreased the arrhythmia in Case 2, but did not abolish it. Following effective surgical treatment of hyperthyroidism the arrhythmia completely disappeared.

THE SKIN CAPILLARIES IN RAYNAUD'S DISEASE *

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During the last decade, physiologic investigation has revealed many new facts with regard to the activity of the capillaries. Our knowledge is as yet fragmentary and incomplete, but enough has been learned to emphasize the great importance of this portion of the vascular system.

From the standpoint of tonus, the capillaries may be affected either by spastic or contraction reactions, or by atony or dilatation reactions. The clinical manifestations usually include a combination of these capillary responses, although pure reactions are seen. The atonic capillary is usually seen in the so-called vasoneurotic constitutional states, and less often in persons with apparently normal vasomotor mechanisms. Müller¹ has described the capillary picture in the vasomotor neuroses. This varies markedly from the so-called normal capillary. He emphasized the following points:

1 *Spastic and Atonic Reactions of the Capillary*—The tonus of the capillary is evidenced by changes in the lumen of the vessel, either contracted or dilated. Either of these conditions may be uniformly present throughout the field, or may alternate or follow in sequence. Muller believes that these phenomena are due to inherent changes in the loops, and are not a result of arteriolar or venous reaction, since the capillary reactions are variable in contiguous loops. He holds that if changes in the arteriole lumen were responsible, tributary groups of capillaries would behave similarly.

2 *Variation in the Flow and Pressure*—Abnormal flow is evidenced by changes in velocity, periods of stasis and granular stream.

3 *Abnormalities in Morphology of the Loops*—The morphologic variations, he considers of less importance. Abnormally large loops and an abnormally visible capillary venous network are sometimes noted. Parrisi² has described the appearance of the capillaries and contained blood during the stasis periods in abnormal vasomotor states. Muller has described, in Raynaud's disease, large deformed types of loops with gaps in the stream which he attributes to capillary spasm, giving a broken up appearance of the loops.

* From the division of medicine, Mayo Clinic.

1 Muller, L R. Studien über den Dermographismus und dessen diagnostische Bedeutung, Deutsch, Ztschr f Nerven^h 47-48 413-434, 1913.

2 Parrisi^s W. Kapillarstudien bei Vasoneurosen, Deutsch Ztschr f Nerven^h 72 320, 1921.

4 Changes in Capillary Permeability—The changes in capillary permeability cannot be studied by the microscope, but are manifested by scleroderma and other metabolic and structural changes in the skin. Further information can be obtained by studying capillary reactions to different types of stimuli, such as drugs, mechanical and thermic.

In studying the form and behavior of capillaries, it is exceedingly difficult, in certain instances, to determine where the normal leaves off and the pathologic begins. In many apparently normal persons, occasional loops are short and tortuous, dilated or contracted, or are otherwise abnormal. The granular appearance of the flow or the cessation of flow, and plasma gaps, may also be observed in single loops. In the normal person however, these are isolated phenomena. Not until the majority of the loops are abnormal in form and flow are the capillaries classified as pathologic. When a sufficient number of capillaries reveal stasis with dilatation, a definitely recognized cyanosis will exist, and when a sufficient number are empty or only partially filled, pallor of the skin will be recognized macroscopically. As Ebbecke³ has shown, the degree of dilatation of the capillaries and venules determines the color of the skin, while arterial dilatation determines the heat of the skin. In differentiating the pathologic from the normal, the quantitative changes rather than the qualitative indicate disease. Abnormal capillaries in the absence of clinical manifestations, are occasionally encountered.

That the capillaries have an independent contractility seems reasonable. These vessels exhibit responses perhaps more delicate than those of the larger vessels. This would be expected on the basis of structure and function. Anatomic researches have demonstrated contractile or Rouget cells with fine fibrillae wrapped about the endothelial tube. The transitional point from arteriole to capillary, or from capillary to venule, is not always well defined in the vessels of the skin. In lower orders and certain capillaries of mammals the transitional point is definite according to Krogh.⁴ Vasoconstrictor nerves have been demonstrated for certain groups of capillaries. Sufficient confirmation of the existence of dilator fibers is not available. Dilatation of the capillaries has been shown to occur following mechanical, thermal, chemical and hormonal action. It seems reasonable to believe that future work will demonstrate a nervous control of these vessels, similar to those of the larger vessels.

VASOMOTOR NEUROSES

The so-called vasomotor neuroses include a large heterogeneous group of conditions characterized by instability of innervation in the

³ Ebbecke, U. Die lokale vasomotorische Reaktion der Haut und der inneren Organe, Arch f d ges Physiol 169: 1-81, 1917.

⁴ Krogh, August. The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922. Halpert, A., cited by Krogh.

vascular system Cold, moist skin with mild degrees of color changes, varying from marked rubor to cyanosis, usually on the hands, feet or other peripheral areas, may constitute the entire clinical picture Associated low blood pressure, asthenic constitution, and subnormal mental and physical reactions are frequently associated The individuals comprising this group are of the subnormal vasomotor type Their vasomotor responses to various stimuli are usually abnormal, showing either abnormal sensitivity or abnormal reactions to certain stimuli There is probably an underlying congenital basis for these abnormal responses on which are superimposed physical, psychic or infectious trauma, which often brings out the latent instability or abnormal lability of the vasomotor system Buerger⁵ has recently discussed the known facts with regard to the physiology of the sympathetic or vegetative nervous system in a manner to make clear many features of these little understood abnormal states Between the mild and the extreme types of cases, observed in Raynaud's disease, are a large number of intermediate types which cannot be classified with exactitude It seems probable that they differ only in degree, and are expressions of the same underlying pathologic condition This broad clinical conception of the vasomotor neuroses is borne out clinically, and by the study of capillaries Buerger questions the wisdom of too broad a grouping, and believes that the well defined syndrome, as observed in Raynaud's disease, should be retained as a clinical entity

MATERIAL STUDIED

Eight cases, classified in two groups, form the basis of this report Group 1 includes three cases of outspoken Raynaud's disease, characterized by marked color changes with abnormal responses to cold, trophic disturbances, varying from slight trophic excavations on the tips of the fingers to definite gangrene, and pain disturbances Group 2 includes five cases of the more mild conditions in which there was a history of recurring local syncope in the fingers, toes or other distal parts, followed by asphyxia with mild sensory disturbances, such as tingling, burning and numbness The abnormal or inciting action of cold in producing attacks was a marked feature in all cases in this group

METHODS OF STUDY⁶

The capillaries were studied, according to the method of Lombard,⁷ from the standpoint of shape and size, the latter quantitatively by

⁵ Buerger, Leo The Circulatory Disturbances of the Extremities, Including Gangrene, Vasomotor and Trophic Disorders, Philadelphia, W B Saunders Company, 1924

⁶ Brown, G E The Normal Skin Capillary, to be published

⁷ Lombard, W P The Blood Pressure in the Arterioles, Capillaries, and Small Veins of the Human Skin, Am J Physiol 29: 335-362, 1911-1912

measurements of the lengths and calibers of the visible loops and their numbers to the linear millimeter⁸ A stereomicroscope with magnification of 60 and 120 times and eye-piece micrometers with divisions of 0.01 and 0.0025 mm were used for measurements A ribbon filament lamp with heat and color filters gave adequate illumination For finger stabilization, a small iron trough with rubber buffers was quite satisfactory These observations were repeated, in several instances, in the periods of syncope, cyanosis and rubor The capillary flow was studied in respect to the rates of flow in millimeters each second, and appearance and behavior of flow in the different color stages The effects of reduced temperature on capillary flow and skin color were also studied, these will be reported separately Photomicrographs were made in several instances, but not with exact definition, owing to length of exposure time Dr Sheard⁹ of the department of physics has recently perfected this technic, allowing exposures of one-fiftieth second Five other cases showing vasomotor disturbances with sclerodermal changes in the skin are not included in this report because the capillary picture was disturbed by the organic skin changes¹⁰ These cases will be reported in a subsequent study

NORMAL CAPILLARIES

Sufficient observations have been made in studying normal persons of different ages to define fairly definitely the morphologic range of the so-called normal capillary¹¹ (Fig 1) The studies at the Mayo Clinic have shown that the capillary undergoes involutionary changes with advancing age, probably similar to those observed in the larger vessels The capillary apparently becomes longer,¹² the calibers are narrowed, and the increased length may manifest itself as a long, straight or a tortuous loop The usual normal type in the young adult is the hairpin shape, fairly regular and uniform, but there are variations Occasionally, young persons have uniformly thick tortuous loops The absence of narrowed lumina seems to differentiate these from the pathologic tortuous types The greatest difficulty in distinguishing diseased capillaries arises in cases in which the normal and abnormal types are present

8 The nail-fold capillaries are apparently distinctive in that practically all are constantly functioning, thus differing from those in other portions of this tissue

9 Sheard, C Instantaneous Photomicrography of the Skin Capillaries in the Living Human Body, *Science* **10** 409-410, 1924

10 Brown, G E, and O'Leary, P A Scleroderma, to be published

11 Brown, G E, and Giffin, H Z Capillaries and Blood Volume in Polycythemia Vera, *Am J M Sc* **166** 489-502 (Oct) 1923

12 The increased length of the capillary may be more apparent than real, because of increased visibility of the skin with increasing age

in about equal numbers. At best, one observes occasional cases in which no conclusion can be drawn relative to capillary morphology. The average total length of the visible capillary loop in the normal group was 0.42 mm. The average caliber of the arterial limb was 0.007 mm., and of the venous limb 0.009 mm. These are the averages of a group of 110 approximately normal persons from the age of 20 to 95 years.¹³

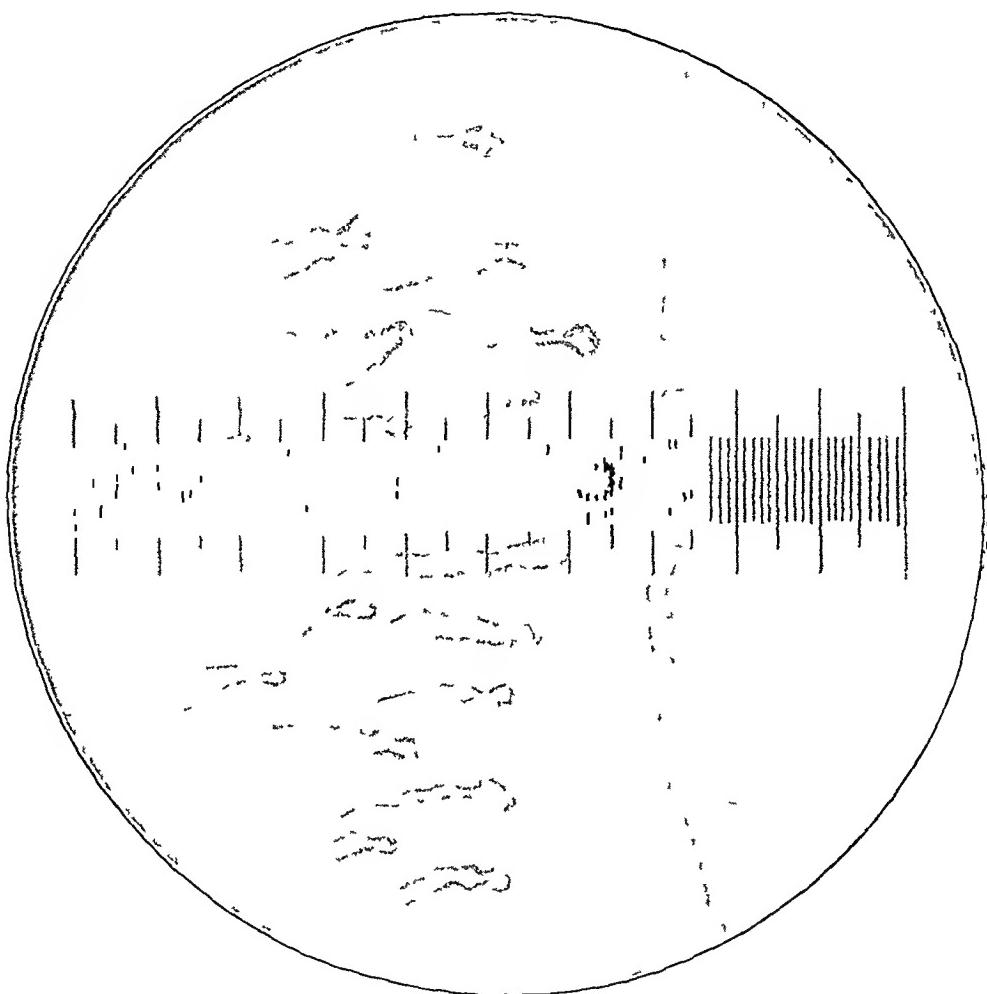


Fig 1.—Normal capillaries. Artist's sketch, scale smallest division, 0.01 mm.

The normality of these persons was based on the absence of demonstrable disease and normal cardiovascular findings for their age.

THE "NORMAL" CAPILLARY FLOW

The capillary flow, in most loops, is usually uniform and rapid at room temperature, from 24 to 26 C. Occasionally, the stream has a

13 The measurement of the length of capillary loops is subject to a moderate error since the arterial and venous terminals are often indistinct and impossible of exact localization.

granular appearance, or there is a short period of stasis in isolated loops. Cold tends to retard the flow, and the period of stasis is longer. The average minimal rate of flow is about 1.5 mm. a second in the normal person.¹⁴ In younger persons the flow is too fast for measurement in most of the loops. The stream is fairly constant, but minor variations in the rate of flow are observed in neighboring loops. There is, however, a fairly well established normal range of flow under constant conditions as regarding hand level in relation to heart, room temperature, and effects of exercise. The observations were made under quite constant conditions and at room temperature ranging from 24 to 26°C. Because of occupation, lack of care of the hands, local irritation of the skin, presence of edema, pigmentation or grime, the nail-fold vessels are occasionally obscured. Excessive manicuring may destroy the arrangement of the distal group of capillaries making an accurate examination impossible. Usually, the fourth and fifth fingers show these effects to a much less degree. One should not form an opinion regarding the capillaries until all the fingers have been examined to see whether the type is fairly uniform. Occasionally, it is impossible to determine whether capillaries are abnormal. In studying the measurements, velocity rates, and so forth, I have always examined all fingers, and selected an area for study which apparently is typical for the majority of the capillaries seen. Rarely, quite different types of capillaries are observed in different fingers.

EFFECT OF COLD ON CAPILLARY FLOW

The effects of heat and cold on skin capillaries are fairly well established in normals. The immediate effect of moderate heat is arterial and capillary dilatation and rapid, uniform flow. The effects of cold vary considerably in different persons. The usual effect of different ranges of lowered temperature to 15°C is slight pallor of the capillary field, due to arterial and capillary contraction which may or may not be observed macroscopically by color changes in the skin, immediate slowing of the stream with moderately segmented appearance of flow due to plasma spaces, the cause of which will be discussed later, and stasis, absent, or very short. The presence of capillary cyanosis is dependent on the degree of capillary dilatation and the length of the period of stasis. After a variable period of recovery, a reaction takes place in which the stream becomes intermittent, showing alternating periods of rapid and slow flow. In persons subject to vasomotor instability, the cold reactions

¹⁴ Capillary flow diminishes in the latter decades of life. This value is for ages between twenty and forty years. Individuals of forty years and under show many capillaries with rates in excess of 1.5 mm. a second and cannot be measured with accuracy.

are similar but more marked, and are present or appear at higher temperatures than are observed in normal persons, in such persons, there is a relative intolerance to cold. When color reactions are present in sufficient degree to be evident macroscopically in the skin, the capillary behavior is pathologic from the clinical standpoint. In the cases of definite Raynaud's disease, the reactions are similar, varying only in degree (Fig 2). Occasional cases of Raynaud's disease show similar stasis reactions to moderate degrees of heat.

THE CAPILLARIES IN RAYNAUD'S DISEASE

Morphologic Changes—One feature which is fairly constant at room temperature is the presence of many wide, dilated atonic types of loops. Occasionally, huge types are seen, with a total length and caliber considerably greater than that observed in normal persons of the same age. These giant types are more common in patients with scleroderma.

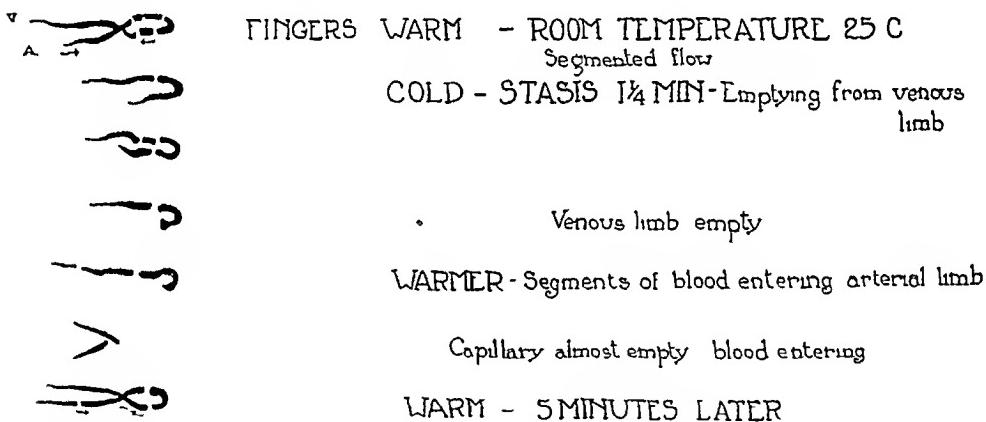


Fig 2—Observations of single capillary in Raynaud's disease, showing effect and recovery from cold.

When gangrene is present, the loops lose their characteristic form, or they may appear as shapeless thrombosed areas, differentiation is often impossible. In the average case, the venous limb is usually dilated more than the arterial limb (Table 1). The caliber of loops changes in the different color phases. I have not observed the branching types oftener than in many so-called normal cases. In the normal, there is a distinct differentiation in the caliber of the arterial and venous limb which becomes accentuated with increasing age. In Raynaud's disease, this differentiation becomes less distinct, and, in many cases, it is very difficult to distinguish the two limbs from the relative size of the calibers. The direction of capillary flow decides this point. The capillary loops at room temperature are usually of broad hairpin type, with or without tortuosity. Patients examined at 25 C and at 15 C show measurable differences in the diameter of the capillary lumen. With lower tempera-

Capillary Studies in Raynaud's Disease

Case	Condition	Loops for length	Total length of capillaries	Average capillary diameter	Control Period, 2 to 25°C	Cyanotic Period	
						Rate of flow	Rate of flow, min for 1 inch second
1	Advanced Raynaud's disease, marked trophic changes	7	0.15	0.0125	Stasis periods from 10 to 15 minutes, then too slow for measurement	Complete stasis	Complete stasis
2	Fairly severe Raynaud's disease, no trophic changes	28	9	0.06	0.012-0.02-0.016	Granular, slow strain, few loops, strain in groups or clusters	0.01-0.006-0.007
3	Severe Raynaud's disease, cyanosis and trophic changes	26	6	0.25	Wide capillary with broad dilated venous limbs	Few loops, show complete stasis	0.02-0.03
4	Fairly mild Raynaud's disease, early scleroderm-like changes	60	0.36	Wide capillary, few loops have lost their form and appear as red blotches	Many loops, complete stasis, wide gaps in stream	0.02-0.03	0.02-0.03
5	Moderately severe Raynaud's disease	34	3	0.21	Slow segmented flow, few gaps	Complete stasis for periods ranging from 20 to 10 seconds	0.02-0.03
6	Moderately severe Raynaud's disease, syncope and cyanosis	23	10†	0.51	Outline of capillaries too broken and ragged for accurate measurement	Complete stasis in all loops for from 1½ to 15 seconds, cyanosis disappears when flow reaches 0.07 mm each second	0.02-0.03
7	Fairly mild Raynaud's disease, local syncope	53	9	0.70	Moderate dilatation of venous limb, arterial limb relatively contracted	Many loops show complete stasis, others very rapid flow	0.02-0.03
8	Mild Raynaud's syndrome, local syncope, no cyanosis	49	12	0.22	No dilatation of arterial or venous limb	Groups of from 3 to 4 loops with slow granular stream or stasis, others with normal flow	0.01-0.006-0.005
Average Normal values		—	—	—	—	—	0.06-0.05

* In this table, ♂ means male ♀ female

† Five open and five partly open

‡ Subject to moderate error since exact terminals of loops cannot be determined

§ Average flow rates in persons under 40 years of age are in excess of 15 mm each second, decreasing with increasing age

Description of Capillaries

Capillaries examined in nail fold, first toe on left foot. Cyanosis? During warm and cold exposure, capillaries deep blue, short thick broad types, no tortuosity

Long broad loops, hairpin type, loops not well defined, rugged in outline, apparent loss of tone, much more marked during cyanosis

Dilated broad loops, hairpin type, no tortuosity, during cold period, complete loss of tone, producing shapeless sines

Broad regular types, arterial limb not contracted as would be expected for a person of this age, regular hairpin types

Regular hairpin loops, many capillaries visible or segment visible, few large dilated atonic forms

Large broad, irregular appearing loops, many loops partly filled during stasis, many broad gaps in stream

Capillary loops resembling normal, usually with normal flow, groups of from 3 to 4 capillaries interspersed with capillaries showing fairly rapid velocities

Capillary loops resembling normal, usually with normal flow, tendency to stasis, slow granular stream and wide gaps in flow

tures, the outline of the loop becomes ragged and indistinct because of capillary dilatation and imperfect filling. Many loops, because of incomplete filling, appear as irregular segments. The color changes from a slight to a marked cyanosis, depending on the duration of stasis. The morphologic changes are not conclusive, and in several cases quite normal appearing loops were observed, but moderate grades of dilatation during the compensated periods were found, in some degree, in all cases in this series.

Capillary Flow.—At 100 m temperature, the capillary loops, in practically all the cases in this series, have shown varying degrees of stasis in few or many loops, varying with the severity of the case. In other loops, the rate of flow is extremely slow, ranging from 0.02 to 0.18 mm a second. The capillaries show varying degrees of cyanosis, depending on the duration of stasis and dilatation of the loops. Microscopic examination of the capillaries of certain persons, who at 100 m temperature have practically normal skin color, reveals varying numbers of loops with marked slowing of the stream, or complete stasis. These changes were not sufficiently marked to produce color changes in the skin. This, I believe, is of important diagnostic significance, since it presupposes the presence of an abnormally labile vasomotor mechanism, which may, in the future, become of clinical importance. In the flow there are many distinct differences from that observed in normal persons. The most striking characteristic is the slow, languid type, the presence of gaps or plasma gaps in the capillary stream, an intermittent flow, alternating stasis and movement of the cells, and cyanosis. The cause of these clear spaces in the stream has been variously interpreted as due to capillary spasm, and waves and plasma gaps. They are apparently not due to localized spasms of capillaries, since they move in the course of the capillary stream much too rapidly for contraction. A capillary wave or pulsation would not show the intermittence of movement which these gaps exhibit. These are probably plasma spaces caused by intermittent arteriolar relaxation, which allows the cells to enter intermittently into the loops. The broken appearance of the stream apparently is not due to agglutination since it is present in the moving capillary stream and exists at the loop entrance. The flow may be seen to stop and move along at irregular intervals, and is not synchronous with the pulse, respiration or any known factor. The blood is seen to enter from the arterial side in rather languid fashion, the cells coming in clumps with clear spaces or gaps between. These abnormal types of flow are observed in single or in multiple groups of capillaries. There is no uniform rate of flow in the loops, one loop may show stasis, another slight movement. The range of velocities in all loops in the well defined cases of Raynaud's disease is much less than that observed in the normal case (Table 1). In

one patient observed (Case 8), a group of five contiguous capillaries had this intermittent granular languid flow in the compensated stage, while in the balance of the loops the capillary flow was fairly normal¹⁵

BEHAVIOR AND APPEARANCE OF CAPILLARIES IN DIFFERENT COLOR STAGES

Stage of Syncope or White Stage—The capillary loops in the syncope period are small, contracted and partially filled, with well

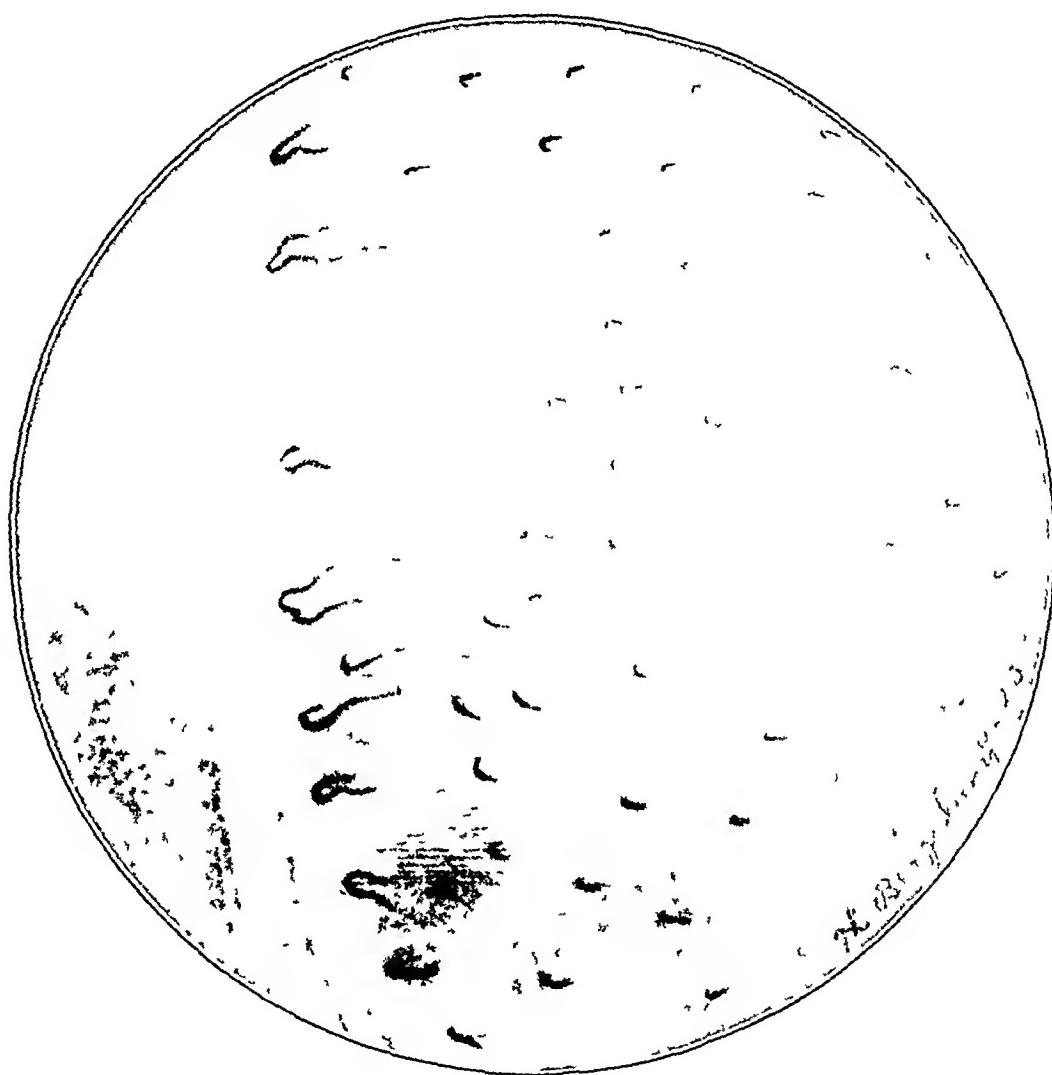


Fig 3.—Appearance of nail-fold capillary in the syncope or white stage, contracted capillaries, which are more marked in arterial limb, many capillaries only partly filled or completely invisible

defined outlines (Figs 3 and 6) Occasional clumps of cells may be seen entering the loop from the arteriole, but in many loops no movement of blood is seen Many loops are unfilled, and are thus invisible

15 There is a seasonal influence on the capillary flow, the pathologic variation being less marked in summer

The pallor of the skin is then due to many empty and partially filled capillaries with cessation of the flow in all, or in a majority of the loops. If a sufficient number of loops contain blood with stasis, these will appear cyanotic and then give a bluish pallor to the syncope stage. The transition from the stage of syncope to that of asphyxia has been observed. The loops, being either empty or partially filled, receive segments of blood from both the arterioles and venules. Large groups

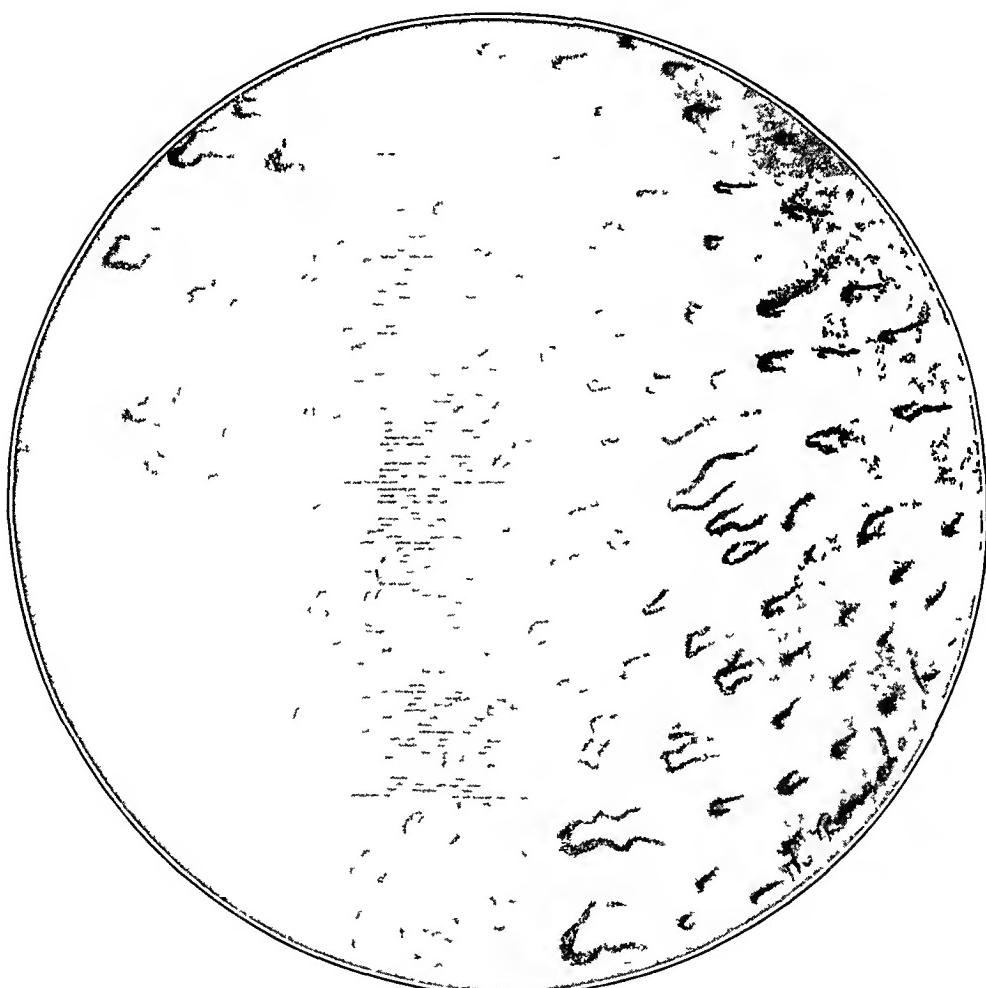


Fig 4.—Same group of capillaries as shown in Figure 3 in stage of cyanosis, increase in number of capillaries with marked dilatation in one group of capillaries, complete stasis of capillary stream with cyanosis of capillary blood

of cells come in gradually from the arterial side, with or without a reflux of cells from the postcapillary venule. The longer the period of stasis, the more marked is the cyanosis and the greater is the dilatation of the loops. The capillary dilates with the blood, filling up the loops in a languid, desultory fashion. A loop may be filled by the blood entering in normal fashion, followed by stasis, dilatation and cyanosis.

Stage of Asphyxia—The loops have a characteristic appearance and behavior in this stage (Figs 4 and 6) They are large, with diameters in many loops twice that observed in the compensated period Dilatation with complete stasis and variable degrees of cyanosis explain the color of the skin In single loops, the blood may move extremely slowly, with one or more plasma gaps Many loops are incompletely filled with mere

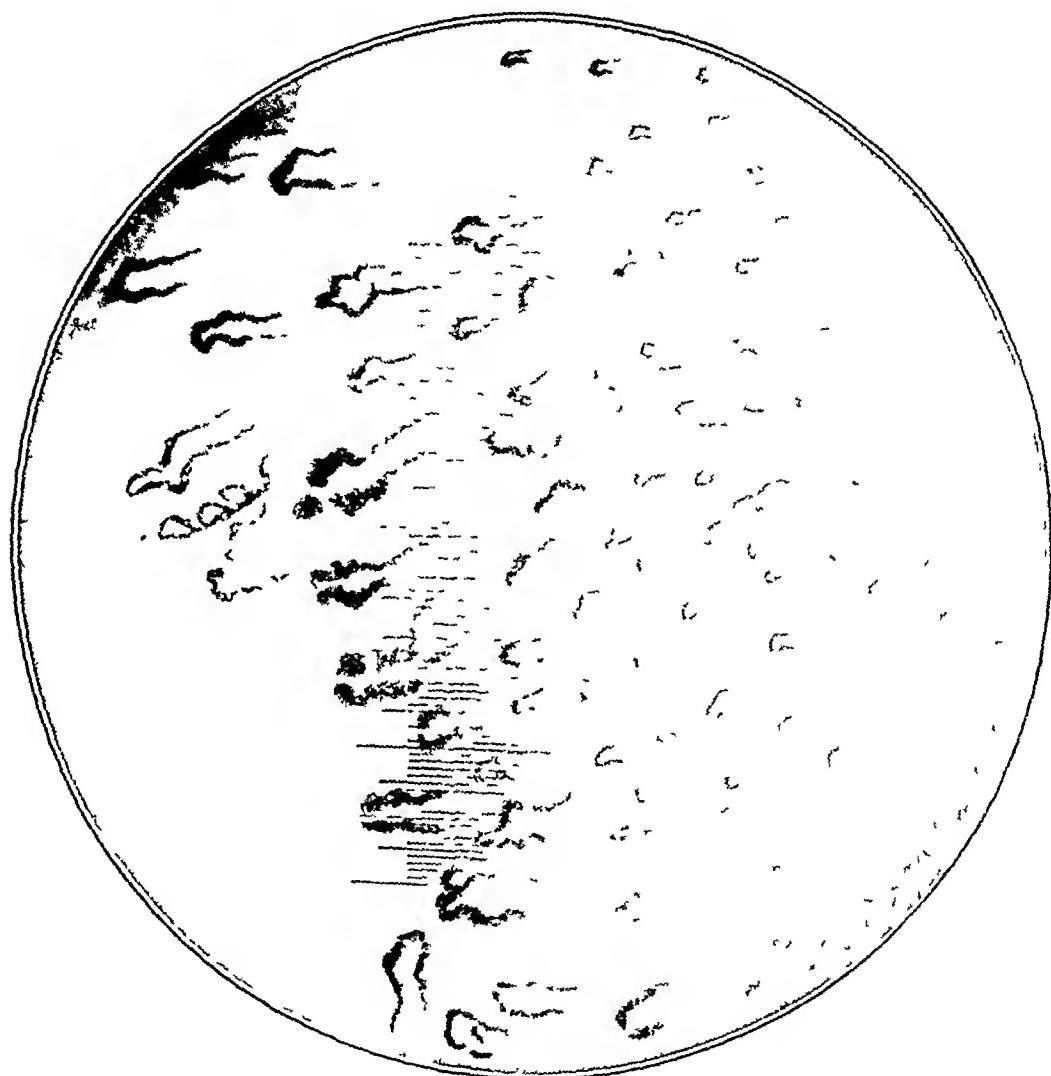


Fig 5—Same group of capillaries as shown in Figures 3 and 4 in rubor stage, well defined capillary outline, continued dilatation of many loops, and broken appearance of loops due to plasma gaps in four contiguous loops, capillary blood is bright red in color in majority of loops

segments of cells The intensity of the stage of asphyxia depends on the period of stasis and the degree of dilatation of the loops As the period of asphyxia wears off, fairly large segments of blood may be seen entering the loops intermittently from the arteriole The flow decreases in direct proportion as the temperature decreases In Case 2, at 15 C, there was complete stasis with deep cyanosis in all loops The period of stasis varies from a few seconds to twenty minutes Symp-

toms, such as numbness, burning and tingling sensations, are complained of and the person will make efforts to restore circulation, either by warming the hands or by exercise. The symptoms seem to have a direct analogy to those observed in the claudication states resulting from a tissue anoxemia. The transition from the cyanosis to the hyperemic period is interesting. In Figures 2 and 7 are shown the differences in the appearance of a capillary loop during the transition from complete stasis to the active capillary flow. The first movement of the stream observed was the emptying of the venous limb into the collecting venule, second, the shifting of a clump of cells in the connecting limb toward the venous side, third, a segment entering from the arterial entrance, and, fourth, an active flow from the arterial side with rapid change from a cyanotic to a bright red blood.

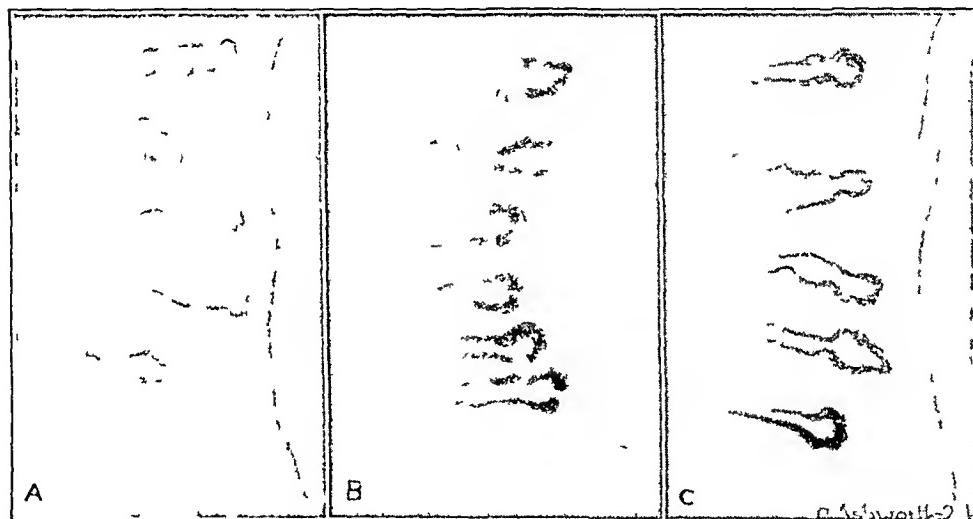


Fig 6.—Capillaries in the three color stages. A, white or syncope stage, partially filled contracted capillaries with absence of arterial limb in several loops; B, blue or cyanotic stage, stasis, dilatation and plasma gaps, and C, red or rubor stage, sharp well defined capillary indicating partial restoration of tone and flow.

Rubor or Stage of Hyperemia.—This stage is due to the resumption of the normal flow and the presence of many moderately dilated loops and of oxyhemoglobin (Figs 5 and 6). This is due to relaxation of arterial spasm and partial restoration of capillary tone. The capillary calibers reduce somewhat, though not to normal diameters, outlines become clearer, the stream in some loops becomes continuous, and in others shows variable speeds. This finding is not uniform, since many of the capillaries will still show varying degrees of stasis or a slow segmented flow. In other instances, alternating short periods of stasis and active flow are observed in the recovery period. There is a definite independence of capillary flow and behavior in the loops. One loop may

show complete stasis, and the next loop, normal flow. However, a fairly uniform behavior is evident in the majority of the loops. In many cases, permanent color changes are maintained in the skin, with slight degrees of rubor, cyanosis or pallor. The color transitions are rarely complete.

COMMENT

It is believed that capillaries and venules can change their lumen independently of the arteries¹⁶. This being true, an explanation is available for the vascular phenomena observed in certain vasomotor disorders. Hooker¹⁷ regards the nervous control as the factor producing capillary tone to balance the chemical factors producing dilatation. Vasodilator nerves for capillaries have not as yet been demonstrated. The veins are apparently supplied with a venopressor mechanism, as shown by Hooker in his experiments on the mesenteric vessels. Other agents affecting capillary tone are metabolic and hormonal in nature. Dale's contributions on histamin have shown it to have a selective toxic action on capillary endothelium causing dilatation and inert flow in these vessels. This substance is a true capillary poison. Krogh has raised the question of the existence of a pituitary extract-like substance that exerts a tonic influence on the capillaries. Although there is much to learn with regard to the physiology of the capillaries, sufficient data is available to permit a rational explanation of the phenomena observed in these vessels in vasomotor states.

In health, there is a finely balanced coordination of the different components of the vascular tree, as evidenced by noting the effects of cold on vascular flow in the skin, the immediate effect of which is arterial constriction with diminished blood supply to the capillaries. These vessels contract synchronously, since dilated capillaries with contracted arterioles would serve no useful purpose. Compensation is evidenced by arteriole relaxation with increased arterial flow, the capillaries revealing a similar response. From observations of the venous portion of the capillary loops, it may be assumed that the venules are behaving similarly. There is a close relationship of the vegetative or sympathetic nervous system to the cerebrospinal nerves in spite of the fact that these activities are distinct. W J Mayo¹⁸ has raised the question, in a recent

16 Cotton, T F, Slade, J G, and Lewis, T. Observations Upon Dermatographism with Special Reference to the Contractile Power of Capillaries, *Heart* **6** 227-247, 1917. Dale, H H, and Laird, P P. Histamin Shock, *J Physiol* **102** 355-390 (March) 1919. Dale, H H, and Richards, A N. The Vasodilator Action of Histamin and of Some Other Substances, *J Physiol* **52** 110-165 (July) 1918.

17 Hooker, D R. The Functional Activity of the Capillaries and Venules, *Am J Physiol* **54** 30-54 (Nov) 1920.

18 Mayo, W J. Coordination of Human Vegetative Functions, *Surg, Gynec & Obst* **38** 312-317 (March) 1924.

paper, whether many of the pathologic phenomena, which we interpret as evidence of nervous or functional disorders, are not the result of the more recently acquired central nervous system attempting to control the vegetative activities. It would seem possible to extend this inquiry more specifically to the vasomotor neuroses, and ask if these manifestations are not the result of an attempted control on the part of the psychic spheres. Conversely, it might be questioned whether the vegetative system might not attempt abnormal control when psychic factors apparently play no rôle. The incidence of psychic factors in precipitating the symptoms of Raynaud's disease is noteworthy. The local manifestations of blushing attest to the close interrelationship of the psychic and vasomotor activities.

The phenomena exhibited in the Raynaud type of the vasomotor neuroses indicate an abnormal sensitivity to certain stimuli, and incoordination on the part of the various components of the vascular field.

The syncope phase of an attack of Raynaud's disease is due to an excessive contraction of all three vascular elements in the skin. No blood is seen entering the capillaries, the loops are contracted and contain none or only small amounts of blood. The venules are usually invisible. The process may be quite uniform, and consists of a hyperirritable response of the vessels or the vasomotor nerves, usually, to cold, more rarely, to psychic or other stimuli. It is an exaggerated normal response. The production of color changes in the hands by the application of cold to distant portions of the body apparently proves the rôle of vasomotor nerves in this condition. There is a lowered vasomotor threshold for certain stimuli.

The stage of asphyxia reveals the loss of coordination between the capillaries and the arterioles. The arteries still remain contracted, but a reaction of intermittent relaxation has been initiated which allows small segments of arterial blood to enter the loops. The venules are apparently undergoing similar reactions since, at this stage, a reflux of blood takes place into the capillaries. This would seem to indicate intermittent contraction or relaxation of the venules. The capillaries lose their tone and dilate, the degree of cyanosis being apparently proportionate to the length of a period of stasis. The flow is static, and a high carbon dioxide content is evidenced by the change of color of the capillary blood from red to various shades of cyanosis. The dilatation seems to precede the cyanosis, apparently standing in no direct relationship to carbon dioxide content. Other metabolites may cause the loss of capillary tone. There are no data as yet to indicate the nervous mechanism in the production of the capillary dilatation. The lack of balance between the capillaries and arteries may be of physicochemical rather than nervous origin. Contraction of the venules could be assumed by the behavior of the

capillary to cold. In Figure 7 (third observation), the blood leaves the venous portion of the loop independently of movement of blood in the arterial limb. The agglutination phenomenon, as described by Krogh, apparently occurs, and segments of blood pass into the venule. Whether this indicates relaxation of venule contraction or localized capillary contraction is not clear. The former seems more likely, although Krogh does not admit the existence of contraction of the subcutaneous veins.

When the rate of flow is less than 0.1 mm. a second, a flow so slow as to include a definite period of stasis, cyanosis will be recognized in the capillary blood. This point has been designated as the threshold of cyanosis. The skin of persons with evidence of vasomotor instability, whether mild or severe, may become, at room temperature, cold, moist or cyanotic, indicating decreased arterial flow with dilatation of the

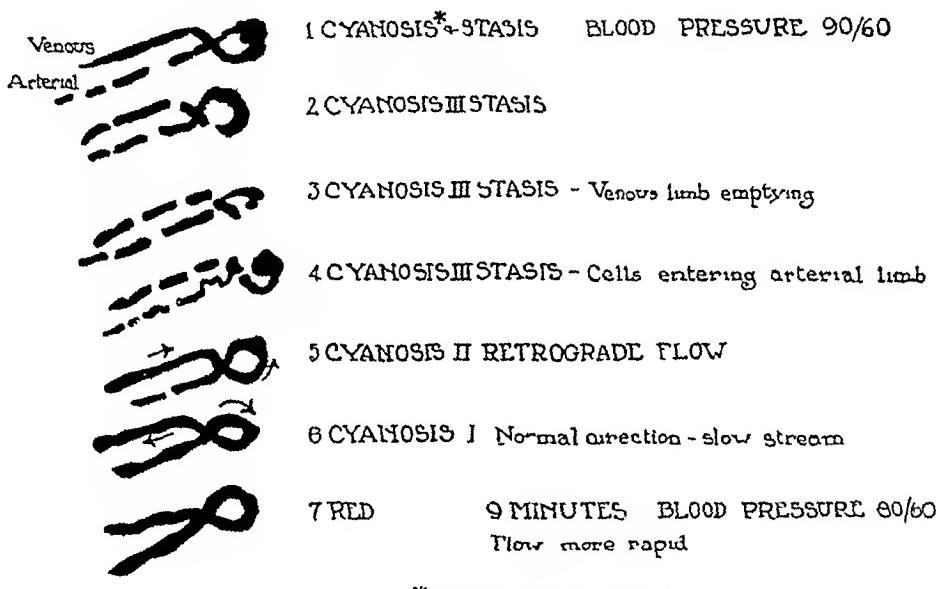


Fig 7.—Observations of single capillary in Raynaud's disease, showing transition from cyanotic to hyperemic stage.

capillaries, and a low cyanotic threshold. Whether the maintained loss of tonus in the capillaries and increased tonus in the arterioles is due to a nervous or physicochemical disturbance is not clear.

The presence of hypotension in the majority of such persons is interesting in the light of arteriolar constriction and a consequent increased peripheral resistance. Low blood pressure is not a necessary factor in these cases, as we have observed two cases of Raynaud's disease in which there was a definite hypertension. The low blood pressure may be related to the limited area of arteriolar constrictor action, or to the decreased resistance to blood flow, due to the dilated capillary bed. The sum total of these two forces may, in terms of blood pressure, represent decreased values in the majority of instances.

The independence of capillary behavior seems reasonably certain because of the lack of uniformity of tone and flow in the contiguous loops. One capillary may show complete stasis, the next loop, normal flow, and a narrow loop, very slow flow or stasis. This individual behavior of the loops may not be entirely of capillary origin, as the pre-capillary arteriole and postcapillary venule may contribute to the effect. It is not certain that one arteriole always breaks up directly into a group of capillaries. What were apparently arterioles have been observed in exceptionally transparent skins, in which the precapillary arteriole was of appreciable length and was apparently tributary to one capillary. The transition of arteriole to capillary was not clearly defined. One is not justified in eliminating the precapillary and postcapillary vessels as active factors in the apparent autonomous activity of the capillaries in the skin.

In a case of Raynaud's disease, more direct visual evidence of the independent behavior of the capillary was demonstrated by the following experiment. An individual capillary was selected in which there was stasis and the loop narrow and contracted. By means of a fine glass rod, the loop was touched and dilatation preceded resumption of the flow on repeated observations. Apparently, following mechanical stimulus, and in the absence of increased intracapillary pressure, definite dilatation of the capillary takes place.

In Raynaud's¹⁹ original description of the disease which bears his name, his explanation of the probable behavior of the capillaries fits closely with the modern explanation of the vascular phenomena. The contraction of the capillaries was assumed on the basis of clinical observation and logical conclusions drawn therefrom. He explained the appearance of the stage of asphyxia as follows:

The vessels which return first to their normal caliber, or even beyond, are naturally those which present in their structure the fewest contractile elements, viz., the venules. At the moment when these are opened, the arterioles being still closed, the venous blood flows again into the finest vascular division, and then the extremities will take on that tint varying from blue to black, which is a certain index of the presence of venous blood in the capillary network.

SUMMARY

The skin capillaries in eight cases of Raynaud's disease were studied during the different color phases exhibited by this disease. In the normal compensated periods, many of these vessels disclose evidence of disturbed capillary tone, abnormal flow or complete stasis. The degree in which these abnormalities exist determines in a large degree the color of the skin. The stage of syncope reveals many empty or partially

19 Raynaud, Maurice. On Local Asphyxia and Symmetrical Gangrene of the Extremities, Selected Monographs, London, New Sydenham Society, 1888.

filled contracted loops with stasis. The period of asphyxia is due to refilling of the capillary loops from segments of arterial or venous blood, or both, and dilatation of the loops with varying periods of stasis which determine the degree of cyanosis. The longer the cessation of capillary flow, the more pronounced is the capillary dilatation, and the greater the carbon dioxide content of the capillary blood. The recovery, or rubor phase, is due to resumption of capillary flow, more complete opening up of capillaries, pressure of oxyhemoglobin, and partial recovery of capillary tone. Additional evidence is presented to prove the existence of independent behavior of the skin capillaries.

CLINICAL STUDIES OF DIGITALIS

II TOXIC RHYTHMS, WITH SPECIAL REFERENCE TO THE SIMILARITY BETWEEN SUCH RHYTHMS IN MAN AND IN THE CAT *

DREW LUTEN, MD

ST LOUIS

Numerous investigators have observed certain toxic effects of digitalis on the hearts of animals, and clinicians have assumed that the results thus recorded are generally transferable to patients. These experimental findings are not entirely constant with different species. Their importance would obviously be enhanced if it could be shown just how far the effects produced by the drug on a certain animal parallel its effects on the human heart, and it would be of especial clinical value to know in what animal the toxic effects are most like those that are produced in man. For there is no exact knowledge of the quantitative effects of toxic doses of digitalis on the human heart, because it is only when a patient accidentally receives an excessive amount of the drug that clinical records showing its toxic action are obtained. So far as knowledge acquired in this way confirms the results of pharmacologic investigation, it strengthens the inferences which experimentation affords.

The recent tendency to give digitalis in large dosage has apparently multiplied the number of instances in which toxic amounts of the drug have been administered to patients. In a recent paper,¹ I reported the therapeutic effects produced by administering rapidly large amounts of the tincture of digitalis to a series of about forty patients with normal cardiac mechanism. Toxic rhythms of short duration were observed in four of these patients. The gravity of the symptoms attendant on these toxic rhythms varied in proportion to the apparent gravity of the change in cardiac mechanism. Taken as a whole, these records present a striking parallel between the toxic effects of digitalis on the heart of man and the toxic effects which the drug has been shown to produce on the heart of the cat. The parallel is of obvious importance to experimental investigation and to clinical knowledge. It emphasizes, furthermore, the dangers that may accompany rapid digitalization. For these reasons, electrocardiograms that show certain effects of excessive quantities of digitalis on these four patients are presented, together with the accompanying clinical records.

* From the department of internal medicine, Washington University School of Medicine

1 Luten, Drew. Clinical Studies of Digitalis, I, Effects Produced by the Administration of Massive Dosage to Patients with Normal Mechanism, Arch Int Med 33 251 (Feb) 1924

Robinson and Wilson,² in studying the progress of events that occur when the heart of the cat is progressively poisoned by digitalis, found that there is rather a definite sequence in the manifestations of the action of digitalis on the cat's heart when successive portions of the lethal dose are regularly administered and the administration continued until death takes place. In their experiments, certain phenomena made their appearance after rather definite percentages of the lethal dose had been given. This sequence of events which represents increasing degrees of effect and of toxicity they found to be as follows. First, inversion of the T wave of the electrocardiogram occurred. After additional amounts of the drug were administered, depression of the atrioventricular conduction made its appearance. At about this time, there was some slowing of the heart rate which came on gradually. After still larger amounts, there was an increase in the rhythmicity of the auricles and of the ventricles (producing acceleration of both). The ventricular rate soon exceeded that of the auricles, thus producing atrioventricular dissociation. At about this stage, idioventricular complexes made their appearance. Independent ventricular rhythm with abnormal ventricular complexes developed. This was soon followed by ventricular fibrillation and death.

The sequence of events that followed the administration of digitalis to the four patients of my series cannot be stated with certainty, because records were not taken at sufficiently frequent intervals. An analysis of the records that were made, however, gives unmistakable evidence that this sequence is closely comparable to that which results from the toxic effects of large doses of tincture of digitalis on the heart of the cat. Certain other features of importance which have to do with the toxic action of digitalis are shown in these records, and certain conclusions regarding the toxic action of the drug on the muscle of the human heart are indicated.

In none of these patients, fortunately, did death result from the administration of digitalis, and in none was ventricular fibrillation recorded. The parallel that their records show between the toxic effects of digitalis on the human heart and those shown by Robinson and Wilson for the heart of the cat is not complete, therefore, but so far as it goes it is remarkably close.

REPORT OF CASES

CASE 1—A man, aged 75, admitted Sept 5, 1922, complaining principally of weakness, had had, perhaps, a little dyspnea for a year, noticeable on walking up hill. Otherwise, he had been in good health until six weeks prior to admission, at which time he noticed that he was weak and had a little fever. Fol-

² Robinson, G. C., and Wilson, F. N. A Quantitative Study of the Effect of Digitalis on the Heart of the Cat, *J. Pharmacol. & Exper. Therap.* **10** 491 (Jan.) 1918.

lowing this, he had a slight cough and sputum, also slight edema of the ankles. He had been taking 20 drops of tincture of digitalis three times a day at intervals until about a week before admission.

On admission, there was considerable cyanosis of the lips and nail beds. The cardiac impulse was rather diffuse and was inside the nipple line. The heart sounds were faint. The liver extended 8 cm below the costal margin. There was slight edema of the legs. The peripheral arteries were considerably thickened and tortuous. The urine showed a faint trace of albumin, there were no casts. The nonprotein blood nitrogen was 31.9 mg., the Wassermann reaction was negative, the pulse, 106, the temperature, 38.2°C. The electrocardiogram showed very small complexes in all leads, and notched Q-R-S complexes in Lead III. The provisional diagnosis was chronic myocarditis, emphysema, arterial sclerosis, passive congestion of the lungs and of the liver, and possible pericardial effusion. The patient weighed about 190 pounds (86.2 kg.).

After six days in bed, he was given tincture of digitalis as follows: September 11, 15 minimis, September 12, 75 minimis in four doses, from September 13 to 19 inclusive, four doses of 20 minimis each every day, a total of 650 minimis in eight days. During the eight days of digitalis administration he had no nausea, no change in pulse rate (the extremes being 80 and 112, the mean being 102), and there was no change in the symptoms. There was slight transitory pain in the left chest September 18 and 22. The course of the illness varied, and the patient died November 24. The necropsy showed tuberculous, serofibrinous pericarditis, about 600 cc of fluid in the pericardial sack, marked chronic fibrous myocarditis, calcification and occlusion of the right coronary artery, chronic passive congestion of the liver, spleen and lungs, ascites, and chronic diffuse nephritis.

The electrocardiogram, taken September 19, after 590 minimis of tincture of digitalis, showed atrioventricular dissociation, the auricular rate being 90, the ventricular rate, 96. The type of complexes was essentially the same as before digitalis administration. The electrocardiogram taken the next day, after 60 minimis more of tincture of digitalis, showed atrioventricular dissociation, the auricular rate being 160, the ventricular rate, 90. Digitalis had been discontinued before this record was made. The electrocardiogram taken twenty-four hours later, September 21, showed atrioventricular dissociation, the auricular rate being 93, the ventricular rate, 95. Subsequent records showed a normal mechanism, but with a lengthened P-R time, and a lowered T wave in Leads II and III for some days. There were occasional extrasystoles on admission and afterward. Digitalis apparently did not influence their frequency. Aside from the electrocardiographic records there was no indication, symptomatically or objectively, of effect from digitalis administration.

Large doses of digitalis produced atrioventricular dissociation with an auricular rate of 90 and a ventricular rate of 96. Increased dosage produced an auricular rate of 160 with a ventricular rate of 90. With subsidence of digitalis effect, the auricular tachycardia disappeared, but the ventricular rate remained high and atrioventricular dissociation persisted. With further subsidence of the effect of the drug, the mechanism became normal but showed the usual electrocardiographic evidences of therapeutic dosage. There was no symptomatic evidence of toxic or of therapeutic action of the drug.

The amount of digitalis administered was too great. It produced a serious toxic rhythm. This occurred without nausea and without any evidences of effect that could be noted at the bedside.

CASE 2—A woman, aged 23, was admitted, Aug 17, 1922, complaining of "dipsy," palpitation, cough and dizziness. Her illness began after a forceps delivery, three months previous to admission, with dyspnea, cough, palpitation, and swelling of the abdomen. She had been taking a "patent medicine" for two months previous to admission, but had taken no medicine from a physician in that time.

Conspicuous cyanosis, general anasarca, ascites and dulness at the bases of the lungs were noted. The liver extended 9 cm below the costal margin. The heart was greatly enlarged. At the apex, a systolic murmur, transmitted over the precordium, and a short diastolic murmur were heard. A systolic and diastolic thrill was felt at the apex. The blood pressure was 165 systolic, 100 diastolic. The urine showed a large amount of albumin and many casts. The vital capacity was 450 cc. The electrocardiogram on the day of admission showed auricular fibrillation and a persistent bigeminy. The ventricular rate

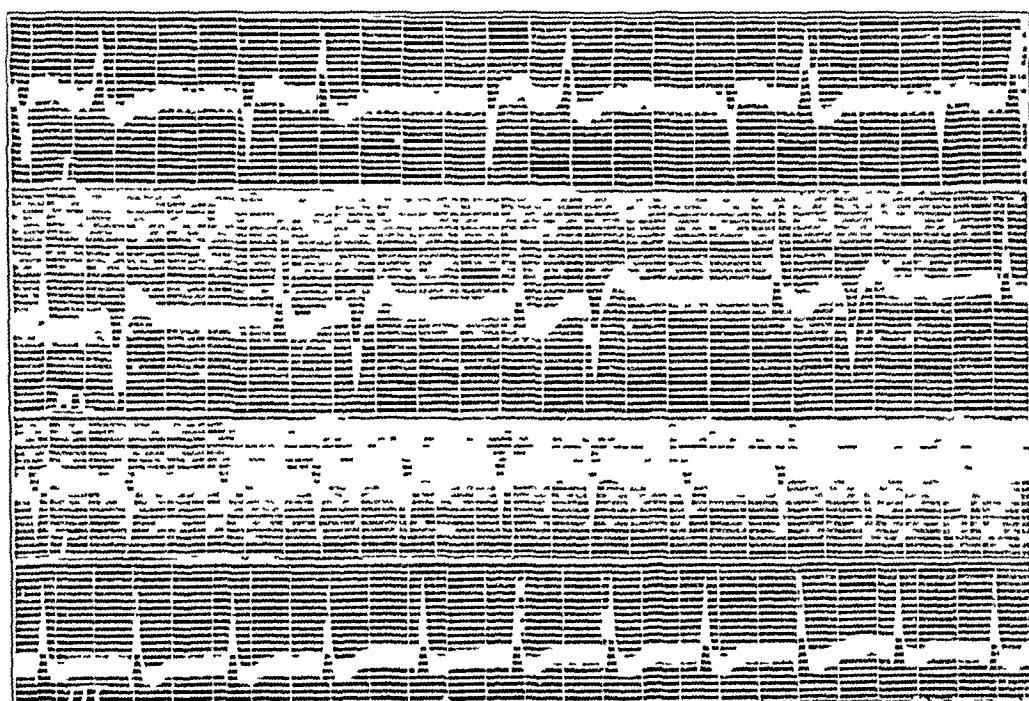


Fig 1 (Case 2)—Upper Leads I and III, Aug 18, 1922, the day after admission (Lead I is distorted by extraneous current), lower Leads I and III, August 19.

was 110. The diagnosis was cardiac decompensation, cardiae hypertrophy and dilatation, auricular fibrillation, premature contractions, mitral disease, and congestion of the liver, lungs and kidneys. The patient's weight was about 85 pounds (38.6 kg).

Because of the electrocardiographic evidence of the action of some toxic agent, such as digitalis, on the heart, no digitalis was administered for thirty-three days. The patient made some, but not great, symptomatic improvement while at rest and on a restricted diet. The cardiae mechanism was normal, August 19 (Fig 1, lower part), the rate being 125. Frequent electrocardiograms showed no arrhythmia thereafter until digitalis was administered. August 24, however, the rate was 144, and the mechanism appeared to be atrioventricular rhythm. The mechanism thereafter was normal, the rate remained at about 120 a minute, and the negative deflection of the T wave in Lead III became less pronounced.

September 19, the patient was given 10 cc of tincture of digitalis in three doses. This was followed by considerable symptomatic improvement and

lessening of the edema, there was no nausea. Eight days later (September 27), she was given 20 minimis of the tincture four times daily. This was continued for a little more than five days, during which time she received 440 minimis. October 2, a slight arrhythmia was noted clinically, and digitalis was stopped. There had been no nausea up to this time, but, later, October 3 and 4, moderate nausea occurred. There was considerable symptomatic improvement during the next few days, and almost complete disappearance of edema for the first time since the patient's admission to the hospital. The patient was able to be up and undertake slight exertion, leaving the hospital, October 23.

The electrocardiogram of August 17 is not suitable for reproduction. The one obtained the next day (Fig. 1, upper part) is quite similar to it, but is clearer. Extraneous current gave fine oscillations in Lead I, but Lead III, is free of this disturbance. In it the characteristic undulations of auricular

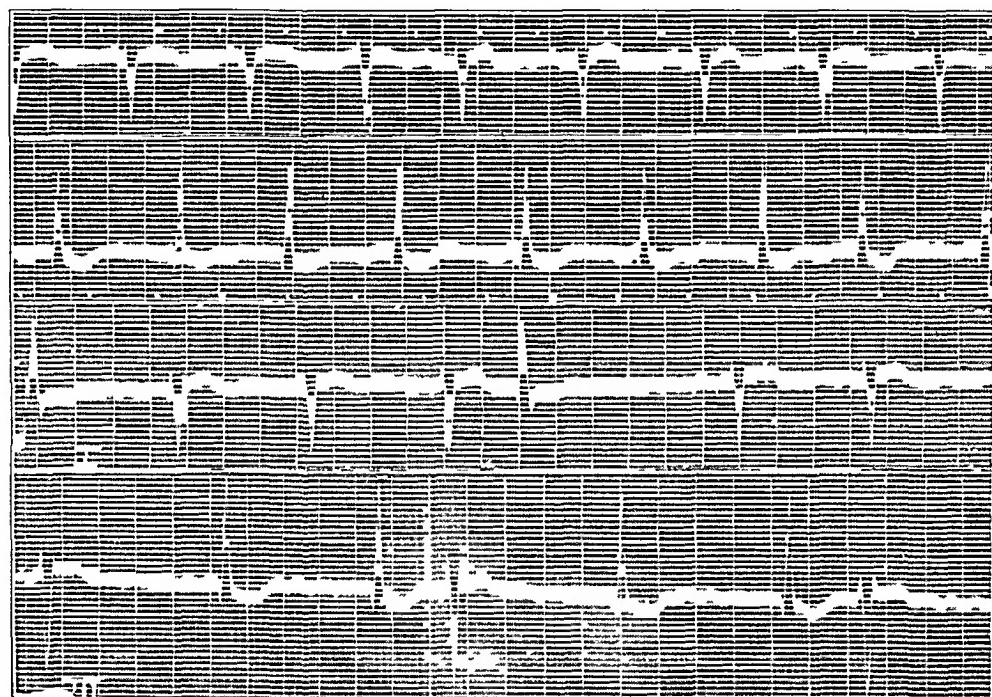


Fig. 2 (Case 2).—Upper Leads I and III, Oct 2, 1922, after 400 minimis of tincture of digitalis in five days, auricular rate, 170, ventricular rate, 92. The position of the auricular beats is indicated by markers. Lower Leads I and III, October 7, auricular fibrillation and frequent coupling.

fibrillation are clearly seen. There is a constant coupling. Comparison with subsequent records shows that the first complex of each couple is of the type that is "normal" for the individual. It consists, in Lead I, of a downwardly deflected Q-R-S group and an upwardly deflected T wave, in Lead III, of an upwardly deflected Q-R-S and a downwardly deflected T wave. The second complex of each couple consists of a Q-R-S group and T wave, both of which are deflected in a direction opposite to that shown in the first complex of the couple. Whether this record represents right ventricular preponderance with an extrasystole of left ventricular origin occurring after each "normal" ventricular beat—the rate of the latter being slowed by a high degree of atrioventricular block—or whether the bigeminy indicates alternate interference with conduction through the left and right branches of the atrioventricular bundle, need not be discussed here. The former would be the usual interpretation. The complexes of Lead II are similar to the corresponding complexes

of Lead III, but of smaller amplitude. The ventricular rate is 107 a minute. Next day, the mechanism was normal. For about a month thereafter and until the administration of digitalis, no abnormal mechanism was noted. The electrocardiogram of October 2, the day digitalis was stopped (Fig. 2, upper part), showed atrioventricular dissociation, an auricular rate of 170, and a ventricular rate of 92. The type of ventricular complexes was essentially the same as before. That the ventricle, though maintaining a high rate independently of the auricle, is still susceptible to auricular influence is shown in the fifth cycle of the first strip. The preceding auricular beat, appearing just before the rhythmic ventricular beat is due, stimulates a ventricular response.

This mechanism was still present on the morning of the next day, October 3, and the ventricular rate was still 92. A few days later, there was a change in cardiac mechanism, which is illustrated by Figure 2, lower part. This shows auricular fibrillation with frequent complexes similar to the second complexes of the bigeminy that was present on admission, the rate being about 82. There was no recurrence of the rhythm composed entirely of coupled beats. The auricular fibrillation persisted. The coupled beats also persisted, but their frequency diminished. The total rate increased a little.

This patient exhibited a toxic rhythm on admission. After the mechanism had been normal for a month, large doses of digitalis produced atrioventricular dissociation with an auricular rate of 170 and a ventricular rate of 92. This occurred thirty-six hours before the appearance of nausea. The dissociation and tachycardia were succeeded by a mechanism much like that observed on admission. The patient's symptoms were of a mildly toxic type, and considerable improvement followed.

The amount of digitalis administered was somewhat in excess of the optimum dose. It was enough to produce increased rhythmicity of both auricles and ventricles. These toxic signs occurred before the appearance of toxic symptoms.

CASE 3.—A man, aged 52, admitted to the hospital, Aug. 22, 1922, had been in the hospital in November, 1921, at which time his complaints were enlargement of the liver, dyspnea and pain in the upper part of the abdomen, these symptoms being of four and one-half months' duration. At his first admission, he showed Cheyne-Stokes' respiration, slight edema of the legs, and an enlargement of the liver to 15 cm below the costal margin. The blood pressure was 190 systolic, 150 diastolic. The heart sounds were weak, the rhythm being regular except for variation with respiration. There was a faint diastolic murmur at the aortic area. The urine contained 4 gm of albumin per liter and many granular casts. The nonprotein blood nitrogen was 57.8 mg per hundred cubic centimeters. The vital capacity was 1,650 cc. The diagnosis was chronic myocarditis, cardiac hypertrophy and dilatation, cardiac decompensation, chronic nephritis, and arterial sclerosis. The body weight was 190 pounds (86.2 kg.). The patient received at that time 20 cc of tincture of digitalis in nine hours. There was prompt diuresis, loss of weight, diminution in the size of the liver, and relief of symptoms. He was discharged greatly improved.

Following this, he had had a somewhat variable course, but, in the main, had been rather well as long as he took digitalis. For a week before his last admission, August 22, he had had some edema of the ankles, slight dizziness and, at times, a little nausea.

There was considerable edema. The liver extended about 12 cm below the costal margin. The heart was regular. There were no murmurs. Other findings were much the same as on the first admission. The electrocardio-

gram showed a low, notched Q-R-S complex in Lead I, the T wave slightly negative in Leads I and II, and the P-R interval 0.2 second. The patient was fairly comfortable and only slightly dyspneic. The body weight was 185 pounds (83.9 kg.).

August 29, seven days after admission, he was given 5 cc of tincture of digitalis at 5 p.m. The next day, he received 5 cc at 10 a.m., 5 cc at 1 p.m., and 2.5 cc at 6 p.m., a total of 17.5 cc in twenty-five hours. Before receiving the last dose, he vomited and felt worse. For a few days following digitalis administration, he was extremely uncomfortable, had almost constant nausea, and looked much worse than before. The urine output was diminished. These symptoms gradually subsided, and there was a conspicuous diuresis of increasing amounts, beginning September 4, and reaching a maximum of 4,300 cc., September 8. The patient improved somewhat about this time, but soon thereafter began to lose ground. Uremic symptoms predominated, and he died November 24.



Fig 3 (Case 3).—Upper left, Leads I, II and III, Aug 29, 1922, just before digitalis administration; upper right, August 30, 11:20 a.m., after 10 cc of tincture of digitalis; lower, Leads II and III, August 31, 10:50 a.m., seventeen hours after 17.5 cc of tincture of digitalis, changed complexes, auricular rate, 131, ventricular rate, 162. The position of the P waves is indicated by markers.

An electrocardiogram, taken one hour and twenty minutes after the second dose of digitalis (Fig. 3, upper right), showed transient ventricular escape, the rate being 83. (This is shown only in Lead II.) Twenty-four hours later, August 31, the record shows persistent atrioventricular dissociation. The rate of the auricle was 131 a minute, that of the ventricle, 162. The form of the ventricular complexes was changed (Fig. 3, lower). In other words, there was an auricular tachycardia and an independent ventricular tachycardia.

The following morning, September 1, the type of ventricular complex was similar to, but not identical with, that just described. The P waves are not clear in this curve, and the auricular rate, therefore, is questionable. The ventricular rate was 108. On the afternoon of that day, the same sort of mechanism was recorded in Lead I, the ventricular rate being 99. Lead II, however, shows an auricular rate of 65, with a ventricular rate of 99. The ventricular complexes occur rhythmically, but show striking variations in form.

September 2 (Fig 4, top), the type of ventricular complex was essentially the same as that which had obtained since August 31. No P waves are visible, and probably both auricles and ventricles were responding to a center in the junctional tissues. Two days later (Fig 4, second strip from top), the type of complex had changed back to the "normal" form, but visible auricular complexes were still absent. The rate, however, had slowed to 87.

The record of September 7 (Fig 4, lower), showed atrioventricular dissociation, with complexes of the original type. There had been further slowing of the ventricle to 77, and of the auricle to 52. On the succeeding day, the mechanism was normal.

This patient, who had previously shown a remarkable improvement after taking 20 cc of tincture of digitalis, was given 17.5 cc within twenty-five hours. There was transient ventricular escape after 10 cc. Through error, 25 cc was given after the patient had vomited. He showed symptoms of severe toxemia. Electrocardiograms showed the

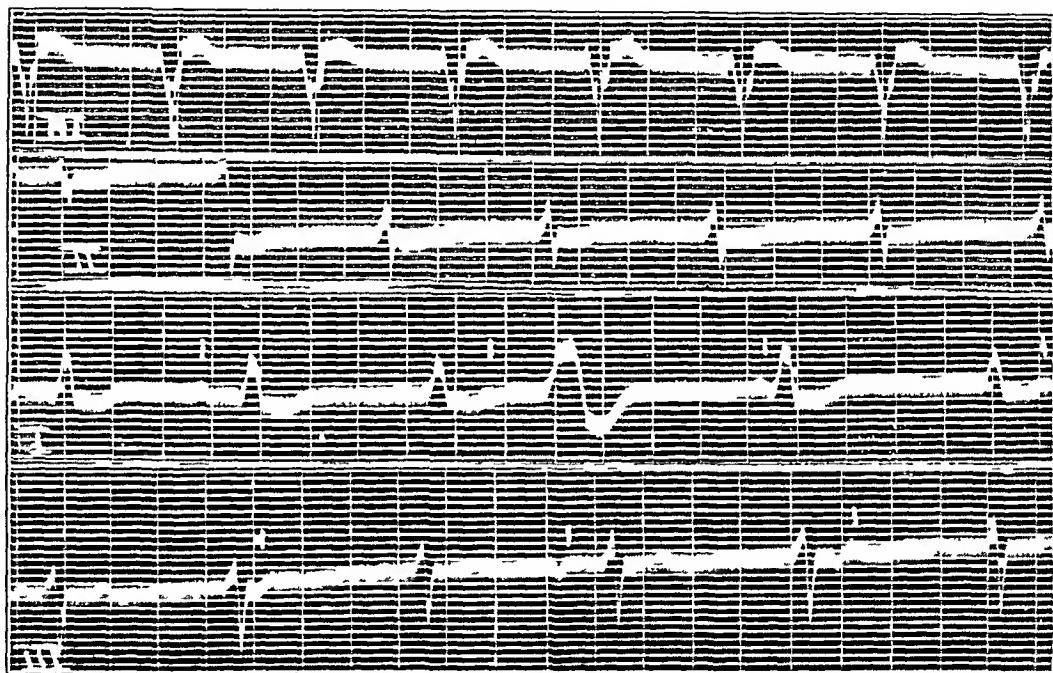


Fig 4 (Case 3)—First strip Lead III, Sept 2, 1922, rate, 97, second strip Lead II, September 4, change in complex to original type, rate 87, third and fourth strips Leads I and III, September 7, atrioventricular dissociation, auricular rate, 52, and ventricular rate, 77.

following succession of events (a) ventricular escape, rate 83, (b) independent ventricular tachycardia, rate 162 with a coincident auricular rate of 131, (c) atrioventricular rhythm, rate 108, (d) atrioventricular rhythm, rate 99, with a quick change to an auricular rate of 65—the ventricular complexes still occurring at a rate of 99 and showing changing forms, (e) atrioventricular rhythm with slowing rate, the type of complex changing back to the original form, (f) further ventricular slowing (77) and atrioventricular dissociation with an auricular rate of 52, and (g) normal mechanism, rate 88.

This was an alarmingly toxic dose. The rhythmicity of the auricles and of the ventricles was increased, that of the latter to such an extent that they instituted an independent rhythm. There was a vagus stimulation, but, in spite of this, the rate of the auricles and of the ventricles was usually high. With increasing elimination of the drug, the heightened rhythmicity of ventricles and auricles lessened, vagus stimulation passed off, and the pacemaker again assumed control.

An independent ventricular rhythm, associated with abnormal ventricular complexes and a rapid rate, is often a precursor of ventricular fibrillation. This result followed, in Robinson and Wilson's experimental work on cats, after the administration of little more of the drug than enough to produce such evidences of intoxication as were shown by this patient.

CASE 4.—A woman, aged 46, admitted, Oct 24, 1922, complaining of dyspnea, edema, dizziness and palpitation, had had slight dyspnea for six years, but only for the past four months had it been very great. During this time, the other symptoms had developed. She had been in bed for two weeks. For three or four weeks prior to admission, she had had no medicine except a "patent" cough remedy.

She was quite dyspneic. There were cyanosis of the lips, considerable edema of the legs and of the abdominal wall, and signs of a small amount of fluid in the right pleural sack. The heart was greatly enlarged to the left. There was a faint systolic murmur at the left sternal border and at the aortic area. There was also a suggestion of gallop rhythm. The urine contained a large amount of albumin and many granular casts. The nonprotein blood nitrogen was 47.7 mg per hundred cubic centimeters, the vital capacity, 800 c.c., the blood pressure, 115 systolic, 95 diastolic. The body weight was 190 pounds (86.2 kg.). The electrocardiogram (Fig. 5, upper left) showed ventricular complexes rather low in all leads, and notched in Lead III, the rate being 96. The diagnosis was cardiac decompensation, chronic myocarditis, cardiac hypertrophy and dilatation, and chronic nephritis.

The patient improved a little during eight days observation, and was then given tincture of digitalis as follows: 10 c.c. at 8 p.m., November 1, 3 c.c. at 8.30 a.m., November 2, and 3 c.c. at noon, November 2. There was an early diuresis beginning on the night of the 1st. Beginning with the night of the 2d, the patient had considerable nausea and vomiting for thirty-six hours. There was no symptomatic improvement for seven days. After this period, she gradually improved and left the hospital, November 28.

The electrocardiogram, taken ten minutes after the last dose of digitalis and, therefore, before its effect on the heart, shows a lengthened P-R interval and a sinus rhythm with a rate of 145 (Fig. 5, lower). This was higher than any rate recorded before digitalis administration.

Figure 6 shows portions of the record made at 10.30 a.m., November 3, twenty-two and one-half hours after the last dose. The three leads were recorded, and immediately thereafter a second record of three leads was made. When the first part of the first of these records was recorded, the auricles were beating rhythmically at a rate of 160, while the ventricles were beating arrhythmically at a rate of 96. There was not complete dissociation, however, between auricles and ventricles, for there were three ventricular responses to every five beats of the auricles. Two out of every five of the auricular contractions produced no ventricular response, while three were able to stimulate the ventricles to contract. The shapes of the three ventricular complexes

follow a certain sequence. The form of the first two is normal, while that of the third is aberrant. The P-R intervals also follow a certain sequence. The interval preceding the first of the normal ventricular complexes is about 0.2 second, that preceding the second is about 0.17 second, while that preceding the abnormal complex is about 0.22 second. These abnormal ventricular complexes, then, are not due to premature ventricular contractions, as might, at first glance, be inferred. Their abnormal form is due to imperfect recovery of the ventricular conducting tracts, the prolonged P-R interval preceding these abnormal complexes is due to a similar defect in the junctional tissues.

Still further evidence of depressed intraventricular conduction is given in that part of the curve recorded later (Fig. 6, lower part). The first part of the third strip of this figure shows the same sequence of events which has just been described. The aberrant complexes are of a form which suggests interference with conduction in the *right* branch of the bundle.³ At the point marked

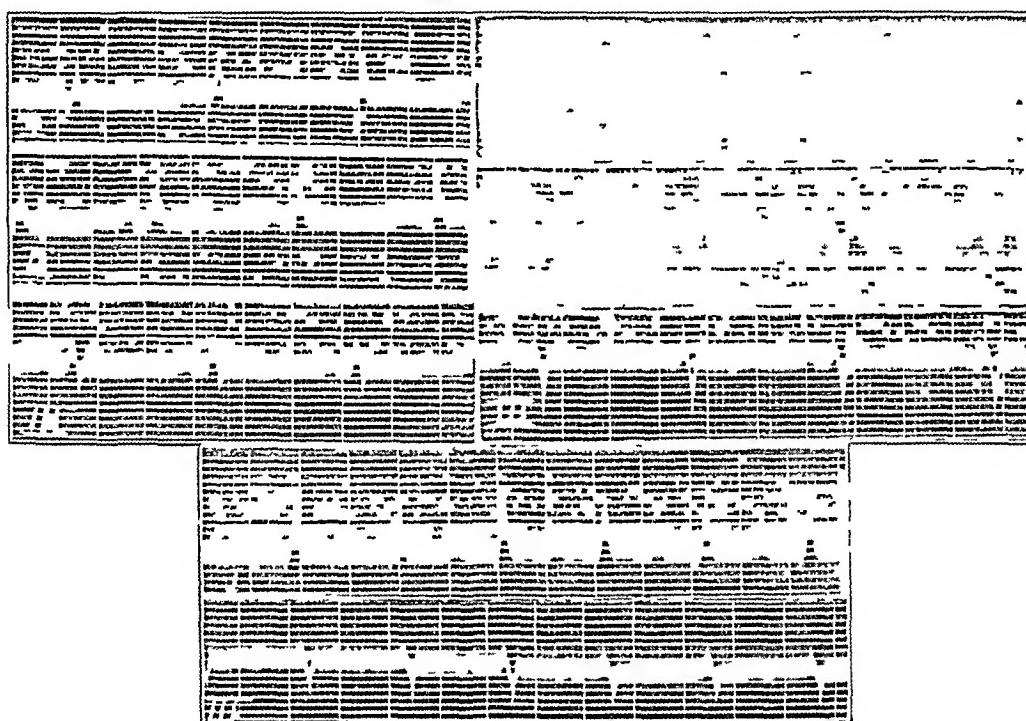


Fig. 5 (Case 4)—Upper left Leads I, II and III, Oct 25, 1922, seven days before giving digitalis, rate, 103, upper right November 1, three hours before, rate, 96, lower Leads I and III, November 2, ten minutes after last dose of digitalis, rate, 145.

R_2 , the ventricular complex is of different type. It has the general outline of those complexes produced by defect in conduction through the *left* branch of the bundle. Following this are two aberrant complexes which indicate an alternation in the facility with which the two branches of the bundle conducted impulses (R_3 and R_4). Further on (R_5), the left branch again is at fault, and, after two more beats, the shapes of the succeeding complexes (R_6 , R_7 and R_8) indicate again an alternation in conduction through the two branches.

These records also show that, for a short time, this patient exhibited an independent ventricular tachycardia. The ventricular rate was 145, the auricular

³ Wilson, F. N., and Herrmann, G. R. Bundle Branch Block and Arborization Block, Arch. Int. Med. 26: 153 (Aug.) 1920, An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, Heart 8: 229 (May) 1921.

rate 170 (Fig 6, second strip) The shape of the complexes is different from that shown before digitalis administration, and they occur rhythmically

Tachycardia was observed clinically at intervals for two days following the administration of digitalis For the third to the seventh days, inclusive, the highest recorded pulse rate was 105, the mean being 90 The next record, taken seven days after the last dose of digitalis, shows complexes of substantially the same form as those recorded just before the drug was given

This woman, weighing 190 pounds (86.2 kg), with considerable edema, myocardial insufficiency and chronic nephritis, received 16 c.c. of tincture of digitalis within sixteen hours There was an early diuresis This was followed by nausea and vomiting for thirty-six hours During the next week, she showed no symptomatic improvement While the patient exhibited toxic symptoms, the following electrocardiographic effects were shown Auricular tachycardia, rate 160 to 170, partial block

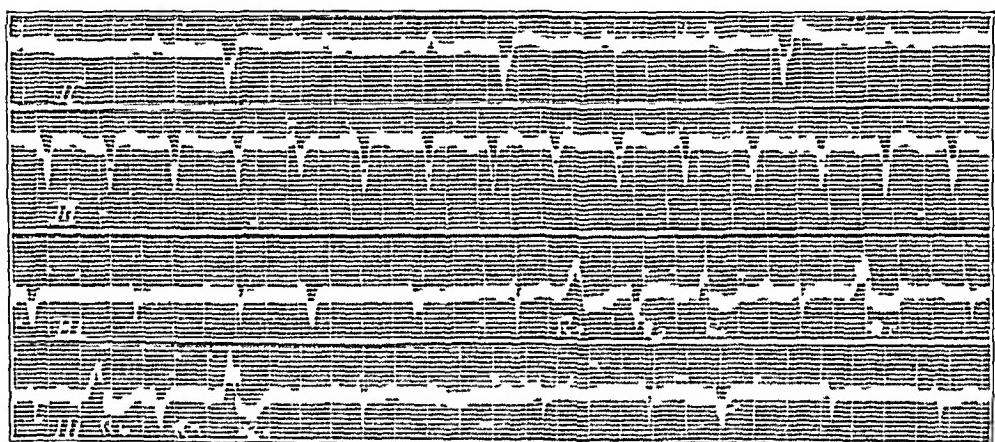


Fig 6 (Case 4)—Nov 3, 1922, twenty-two and one-half hours after the last dose of digitalis, Lead II (first strip) shows an auricular rate of 160 with a ventricular rate of three-fifths as much, i.e., 96, long atrioventricular time preceding aberrant ventricular complexes In the second strip (Lead III), the rate of the auricles is 170, that of the ventricles, 145, position of auricular waves is indicated by markers The third and fourth strips are a continuous record in Lead III, alternation in direction of complexes R₂, R₃ and R₄, and of complexes R₆, R₇ and R₈

with certain atypical ventricular complexes apparently due to depressed intraventricular conduction, auriculoventricular dissociation with an auricular rate of 170 and an independent ventricular tachycardia, rate 145, and depression of conduction through the bundle branches with alternate recovery of the right and left branches After partial elimination of the drug, the cardiac mechanism returned to normal

A beneficial effect was shown after the first dose of 10 c.c. There was a prompt diuresis Following the additional amounts of digitalis, the ventricular tachycardia and the interference with intraventricular conduction gave evidence of serious intoxication of the heart muscle

COMMENT

These four patients all developed auricular tachycardia as a result of digitalis administration. Two of the four showed, coincidently with this auricular tachycardia, ventricular rates between 90 and 100, with complexes of supraventricular form. The other two showed idioventricular tachycardia with abnormal ventricular complexes, the ventricular rates being 145 and 162, respectively. These two patients, who exhibited independent ventricular rhythms with abnormal ventricular complexes, manifested symptoms of much greater severity than the symptoms shown by the two others. It would appear, therefore, from a consideration of these four cases, that toxic doses of digitalis produce on the human heart, when administered in increasing amounts, the following sequence of abnormal mechanisms: auricular tachycardia, increase in the ventricular rate until it exceeds the auricular rate, and independent ventricular tachycardia with abnormal complexes.

The quantitative effect of toxic doses of digitalis on the human heart, it will be observed, closely parallels thus far its quantitative effect on the heart of the cat. Robinson and Wilson² further observed changes in the type of the ventricular complexes, and, finally, ventricular fibrillation. These changes in form of the ventricular complex they interpret as being the expression of impulses arising at different foci. Our patients who exhibited signs of severe toxemia and at the same time showed independent ventricular rhythm gave records which contained also evidence of impaired intraventricular conduction. There is abundant evidence that drugs of the digitalis group do produce such depression of conduction within the ventricle. Robinson and Bredeck⁴ gave this interpretation to the changing ventricular complexes that were recorded in a patient ten minutes after an injection of 1 mg of strophanthin. They further say that this record "is similar to those obtained by Levy and Lewis during this period of so-called potential (ventricular) fibrillation."

Wilson and Robinson,⁵ in commenting on "spontaneous change in the form of the ventricular complex" shown by a patient with complete heart block twenty-three hours after a massive dose of digitalis, offer two possible explanations of the distorted complexes (a) a change in intraventricular conduction, or (b) a change in the location of the pacemaker. It is not always possible to determine which of these causes operates to produce changes in the form of ventricular complexes. Levy and Lewis,⁶ indeed, interpret their curves, to which Robinson and

4 Robinson, G C, and Bredeck, J F. Ventricular Fibrillation in Man with Cardiac Recovery, *Arch Int Med* **20** 725 (Nov) 1917

5 Wilson, F N, and Robinson, G C. Two Cases of Complete Heart Block Showing Unusual Features, *Arch Int Med* **21** 166 (Jan) 1918

6 Levy, A G, and Lewis, T. Heart Irregularities, Resulting from the Inhalation of Low Chloroform Vapor and Their Relationship to Ventricular Fibrillation, *Heart* **3** 99 (Oct 30) 1911

Bredeck make reference, not as evidence of depressed conduction, but as premature contractions arising from a number of separate foci. In our patients, however, the evidence is very strong that the change was produced by variation in conduction through the bundle branches. In either case, the abnormal ventricular complexes shown in our records are an expression of a highly toxic action of digitalis on the hearts of these patients, and the parallel to the action of the drug on the cat's heart is thus extended. The production of ventricular fibrillation, if additional doses are administered after ventricular tachycardia with abnormal complexes makes its appearance, is probable.

SUMMARY

1 Four patients with normal cardiac mechanism developed temporary auricular tachycardia and atrioventricular dissociation after receiving large amounts of digitalis. The ventricular rate was more than 90 in all four cases. In two cases, the ventricular rate was more than 140.

2 The quantitative effects of large toxic doses of digitalis on the human heart thus closely parallels the quantitative effects of the drug on the heart of the cat in increasing the rhythmicity of cardiac muscle.

3 The records of the two cases with independent ventricular tachycardia gave evidence also of impaired conductivity through the bundle branches. This evidence of impaired conductivity within the ventricle gives further support to the view that the effect of additional dosage further parallels the effect shown on the cat's heart in producing ventricular fibrillation.

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CLINICAL STUDIES OF DIGITALIS

III ADVANCED TOXIC RHYTHMS *

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ST LOUIS

In giving large amounts of the tincture of digitalis to a series of patients with normal cardiac mechanism,¹ I observed auriculoventricular dissociation with tachycardia of auricles, of ventricles, or of both, as a toxic effect of the drug in four patients. A comprehensive study of these toxic rhythms² showed a remarkably close parallel quantitatively between the effects in these patients and the toxic effects which were observed by Robinson and Wilson to result when successive fractions of the lethal dose were administered to cats. These authors found that further dosage produced ventricular fibrillation. The drug was stopped about the time of the appearance of these abnormal rhythms in my patients, and further harmful effects, fortunately, were not observed.

While the study of these effects of digitalis was in progress, there were published several reports of abnormal cardiac mechanisms occurring in patients who had been receiving large amounts of digitalis. One peculiar form of ventricular tachycardia, in particular, was reported by Schwensen³ and by Felberbaum⁴. This consisted in a regular tachycardia with an alternate change in the direction of deflection of the Q-R-S complexes. Felberbaum suggested the possible rôle of digitalis as a cause of this unusual mechanism, while Schwensen expressed the conviction that the drug was the causative agent. Possible explanations of the exact mechanism by which this regular alternation in direction of the complexes might be produced were discussed by both authors. The likelihood of its transition into ventricular fibrillation was emphasized by both.

My own observations on the action of digitalis in producing ventricular tachycardia, referred to above, led me to believe that this

* From the Department of Internal Medicine, Washington University School of Medicine.

* Read before the Central Interurban Clinical Club, Dec 1, 1923.

1 Luten, Drew Clinical Studies of Digitalis, I, Effects Produced by the Administration of Massive Dosage to Patients with Normal Mechanism, Arch Int Med **33** 251 (Feb 15) 1924.

2 Luten, Drew Clinical Studies of Digitalis, II, Toxic Rhythms, with Special Reference to the Similarity Between Such Rhythms in Man and in the Cat, Arch Int Med **35** 74 (Jan) 1925.

3 Schwensen, Carl Ventricular Tachycardia as a Result of the Administration of Digitalis, Heart **9** 199 (April 30) 1922.

4 Felberbaum, David Paroxysmal Ventricular Tachycardia, Report of a Case of Unusual Type, Am J M Sc **166** 211 (Aug) 1923.

unusual type of tachycardia was but a more advanced effect of the drug than that shown in the patients of my series². Certain portions of some of the records of my cases presented evidence which seemed to furnish, if not indeed to anticipate, an explanation of that action of digitalis by virtue of which the peculiar tachycardia in question might be produced.

In order to study these questions further, search for similar electrocardiograms was instituted among the records of the heart station of the Washington University School of Medicine at Barnes Hospital. Only two were found which were similar in every respect to the records under consideration. A third showed an alteration in direction of the ventricular complexes but the latter were not entirely rhythmic. (This record is similar to that in another case reported by Schwensen as due to digitalis intoxication, and is somewhat comparable also to certain portions of some of the records of my patients to which reference has just been made.) The histories of the three patients from whom these electrocardiograms were obtained were then consulted. In each case, it was found that the patient had received large amounts of digitalis just before the onset of the abnormal rhythm. All three patients died within a short time after its appearance. The evidence grows more convincing, therefore, that the abnormal mechanism in these three patients, as well as that in the cases reported by Schwensen and by Felberbaum, was induced by digitalis. Still further weight was given to this conclusion, after the study was finished and while the results were being prepared for publication, in a report by Reid⁵. He published an electrocardiogram which shows the transition of a ventricular tachycardia of not unusual type into one with an alternation in the direction of the complexes. This was followed in less than thirty seconds by ventricular fibrillation and death. The patient had just been given digitalis in large amount.

A solution of the second problem, i.e., an explanation of the mechanism which produces this tachycardia with alternation in direction of complexes, is not so easy to reach, and any conclusion in the light of present data would seem to be equivocal. This study, however, affords certain observations which appear to be of importance in trying to reach an understanding of the mechanism by which digitalis produces this peculiar tachycardia. These observations will be presented and briefly discussed below. Preceding this discussion, the histories of the three patients will be given as clearly as their records allow and their electrocardiograms, which exhibit this abnormal mechanism as well as other toxic effects of digitalis, will be shown.

⁵ Reid, W. D. Ventricular Ectopic Tachycardia Complicating Digitalis Therapy, Arch Int Med 33:23 (Jan 15) 1924

REPORT OF CASES

CASE 1—A woman, aged 64, admitted to the hospital, Feb 7, 1921, gave as her chief complaints dyspnea and edema. She had never had rheumatism. For several years, she had had attacks of dyspnea on exertion. For six weeks prior to entrance, she had had increased dyspnea as well as orthopnea and edema.

She was cyanotic. The heart dulness extended 14 cm to the left in the sixth intercostal space. The apex rate was 115, the pulse rate, 73. The rhythm was absolutely irregular. The first sound was impure at the apex, the second sound was followed by a short blowing murmur. The diagnosis was cardiac decompensation, chronic myocarditis, hypertrophy and dilatation of the heart,

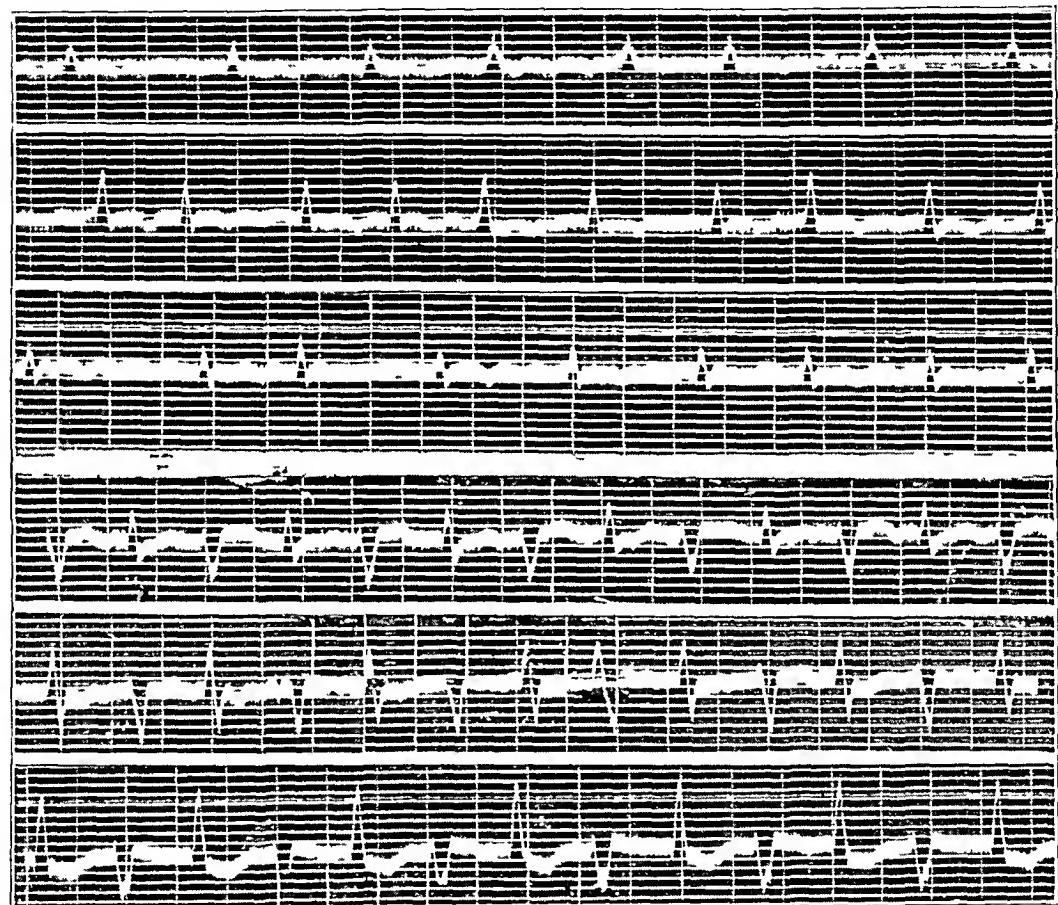


Fig 1 (Case 1)—Upper Leads I, II and III of the record made, Feb 7, 1921, before digitalis administration, lower the three leads the next day, thirteen hours after the administration of 10 cc of tincture of digitalis

auricular fibrillation, hydrothorax, right and left, and edema. At 3 30 p m, the day of admission, the electrocardiogram shown in the upper half of Figure 1 was made. It shows the characteristic features of auricular fibrillation.

The history does not give a clear picture of the patient, but it records that at 7 p m, the day of admission, she was observed to have pinpoint pupils, slow and irregular respirations (six to eight a minute), and that this condition was thought to be due to morphin. She was given caffein sodiobenzoate, $7\frac{1}{2}$ grains (0.48 gm), and strychnin, $\frac{1}{30}$ grain. These drugs were repeated in the same dosage, after forty minutes. At 8 30 p m, she received 1 grain of a proprietary digitalis preparation. The notation was made that this "equals 2 cc of standard tincture." At 9 30 p m, she received $7\frac{1}{2}$ grains (0.48 gm) of caffein sodiobenzoate and $\frac{1}{30}$ grain of strychnin. The apex rate was then

150, the pulse rate, 70 At 10 p m, the respirations were still slow and irregular At that time, she was given 10 c c of tincture of digitalis The next morning at 11 15 (February 8), the electrocardiogram shown in the lower part of Figure 1 was made At noon it was noted that her breathing was "more regular, 25 to 28 per minute" The heart rate was 200, the pulse at the wrist, imperceptible At 9 p m, the same day, she received 5 c c of tincture of digitalis It was noted at that time that she was in a deep stupor, and that the edema had apparently increased Subsequent notes are fragmentary The patient died at 7 50, the following morning

Only the two electrocardiograms shown in Figure 1 were made The one that was made subsequent to the administration of 10 c c of tincture of digitalis shows a regular tachycardia with a rate of 190 The auricular fibrillation still persists The ventricular complexes are deflected alternately upward and downward This record is similar to that shown in Schwensen's second case, and to the one shown in Felberbaum's case It was this similarity which attracted attention and caused me to go over the history so as to discover whether the patient had received a large amount of digitalis just before the making of the electrocardiogram It may be mentioned here that this exact type of curve has been recorded clinically, so far as I am aware, only in patients with auricular fibrillation who had just received large amounts of digitalis

CASE 2—A woman, aged 44, admitted to the hospital, Feb 1, 1922, had as the chief complaints shortness of breath, rapid heart beat and nervousness She had had a goiter for six years During the six months prior to admission, she had been worse and had developed edema and ascites

All lobes of the thyroid were prominent There was considerable enlargement of the cardiac outline The rhythm was absolutely irregular, rate 182 There was moderate edema, and also evidence of ascites The diagnosis was cardiac decompensation, chronic myocarditis, hypertrophy and dilatation of the heart, auricular fibrillation and exophthalmic goiter

The history makes no statement regarding previous digitalis administration She was given 6 c c of the tincture in three doses, the day of admission The drug was continued, 4 c c a day, until February 3, at which time she had received 12 c c It was stopped for twenty-four hours, and then again given, 3 c c a day It is not clear from the record whether it was stopped on February 8 or 9 She had received 24 c c on February 8

The patient's exact condition is not clearly pictured by the history, but definite statements are made that she was improving, February 4 and 6 She began to grow worse, about February 8 She "gradually became weaker," "breathing" became "difficult," and oxygen was administered February 9 There were indications of pneumonia The patient died, the morning of February 10 No necropsy was obtained

The electrocardiogram shown in the left upper part of Figure 2 was made, February 2, after the patient had had 8 c c of tincture of digitalis

It shows auricular fibrillation with a ventricular rate of about 200 a minute There had been a few extrasystoles None was noted, February 4, they were rare, February 6 The right upper part of Figure 2 shows the record of February 7 The ventricular rate had declined to about 150, but the number of extrasystoles had increased The lower part of this figure gives the record made February 8, about the date when the patient began to grow worse She was still receiving digitalis at this time The record shows a ventricular rate of about 125 But it shows also numerous extrasystoles These occasionally are strongly suggestive of coupling

The electrocardiogram shown in the upper part of Figure 3 was made at 11 a m, February 9, that in the lower part was made at 6 p m, the same day The earlier record shows abnormal ventricular complexes of widely different shapes The total ventricular rate is about 165 The later record

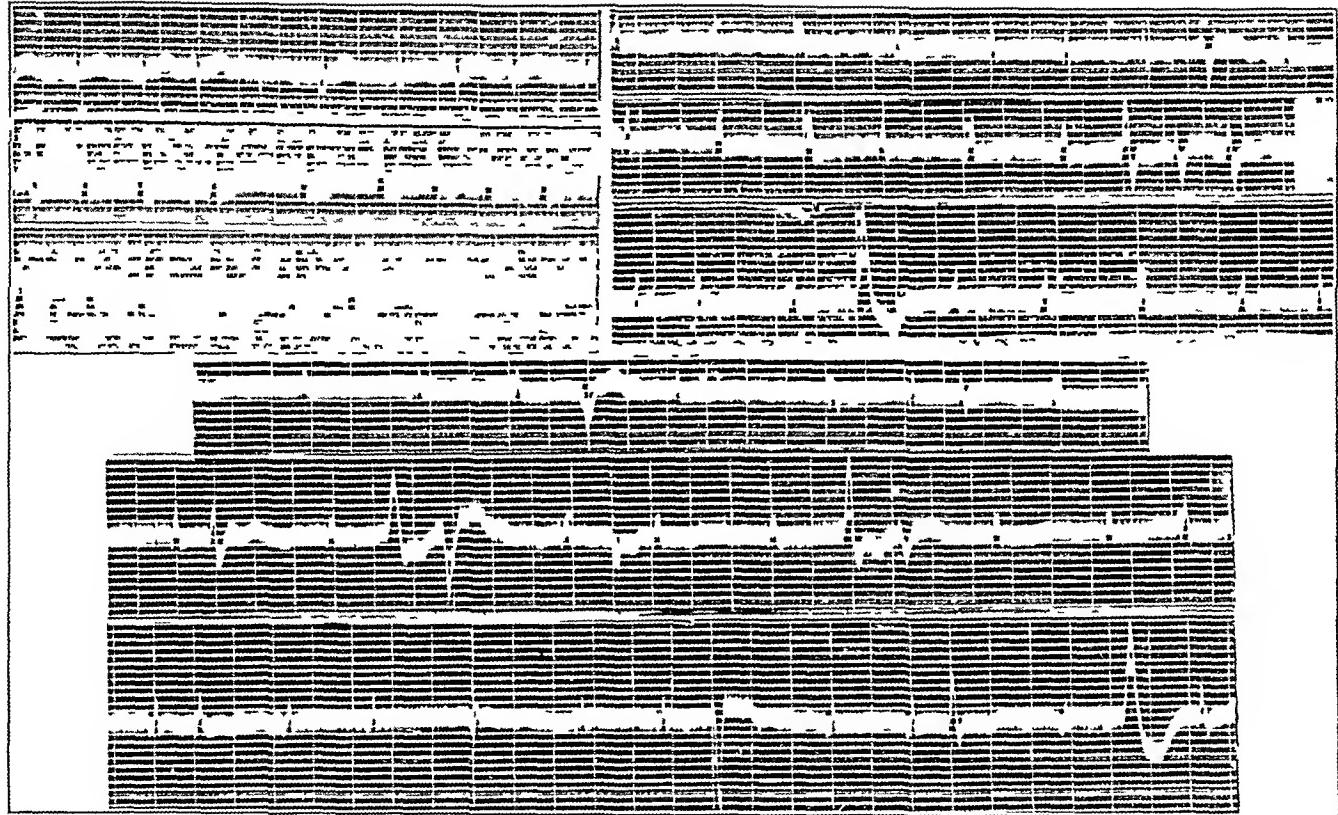


Fig 2 (Case 2)—Upper, left record made, Feb 2, 1922, after 7 cc of tincture of digitalis in twenty-four hours, upper, right record, February 7, after 21 cc of tincture of digitalis in six days, lower record, February 8, after 24 cc of tincture of digitalis in seven days

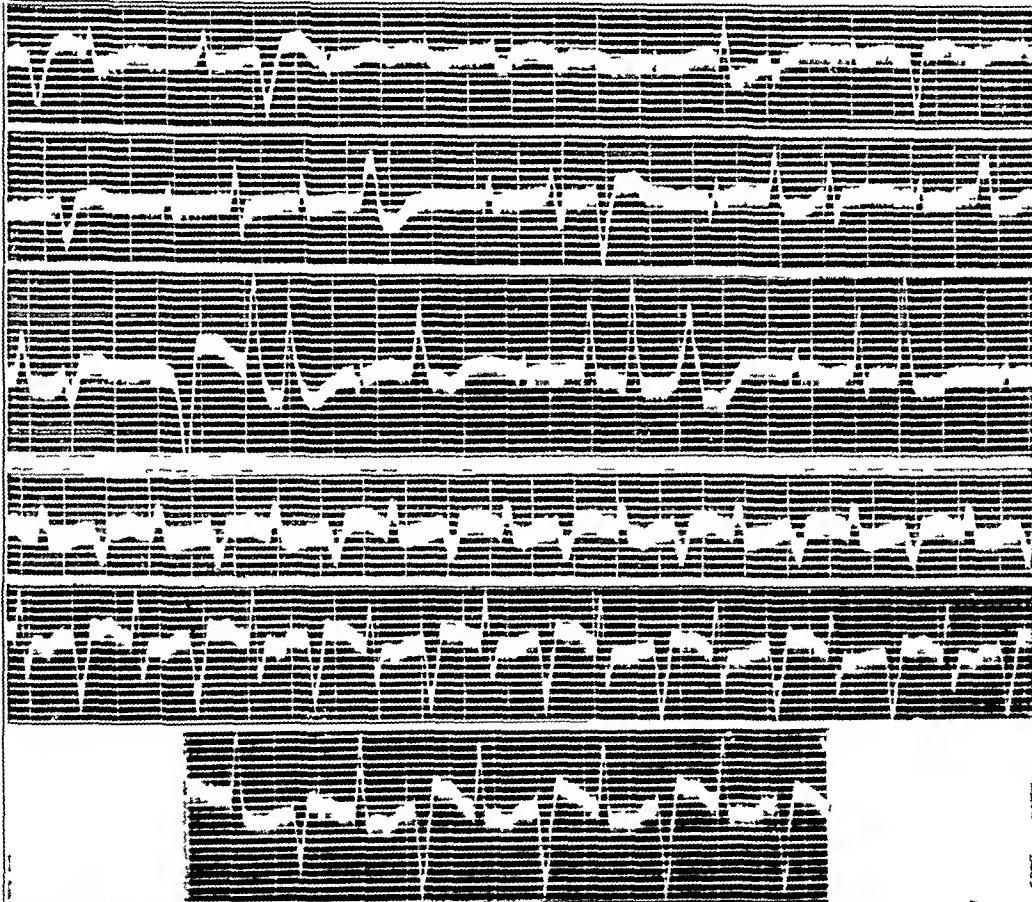


Fig 3 (Case 2)—Upper the three leads, February 9, at 11 a m , lower the three leads the same day, at 6 p m

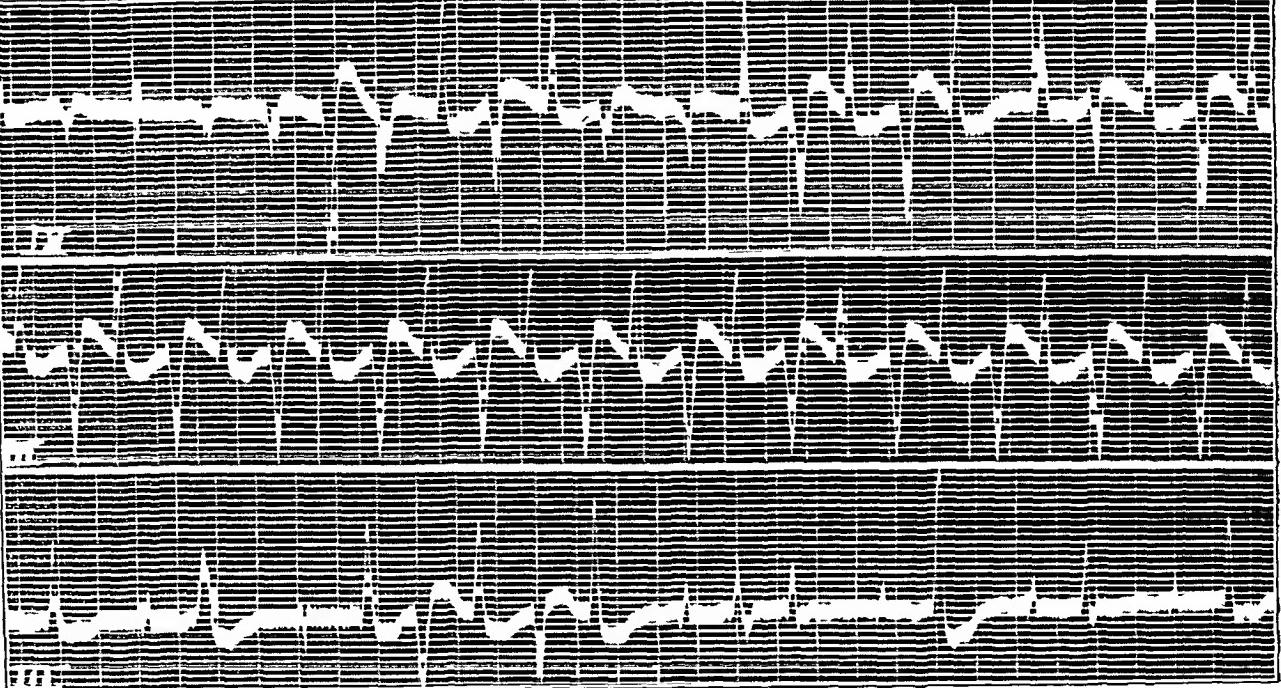


Fig 4 (Case 2) —Lead III, night of February 9

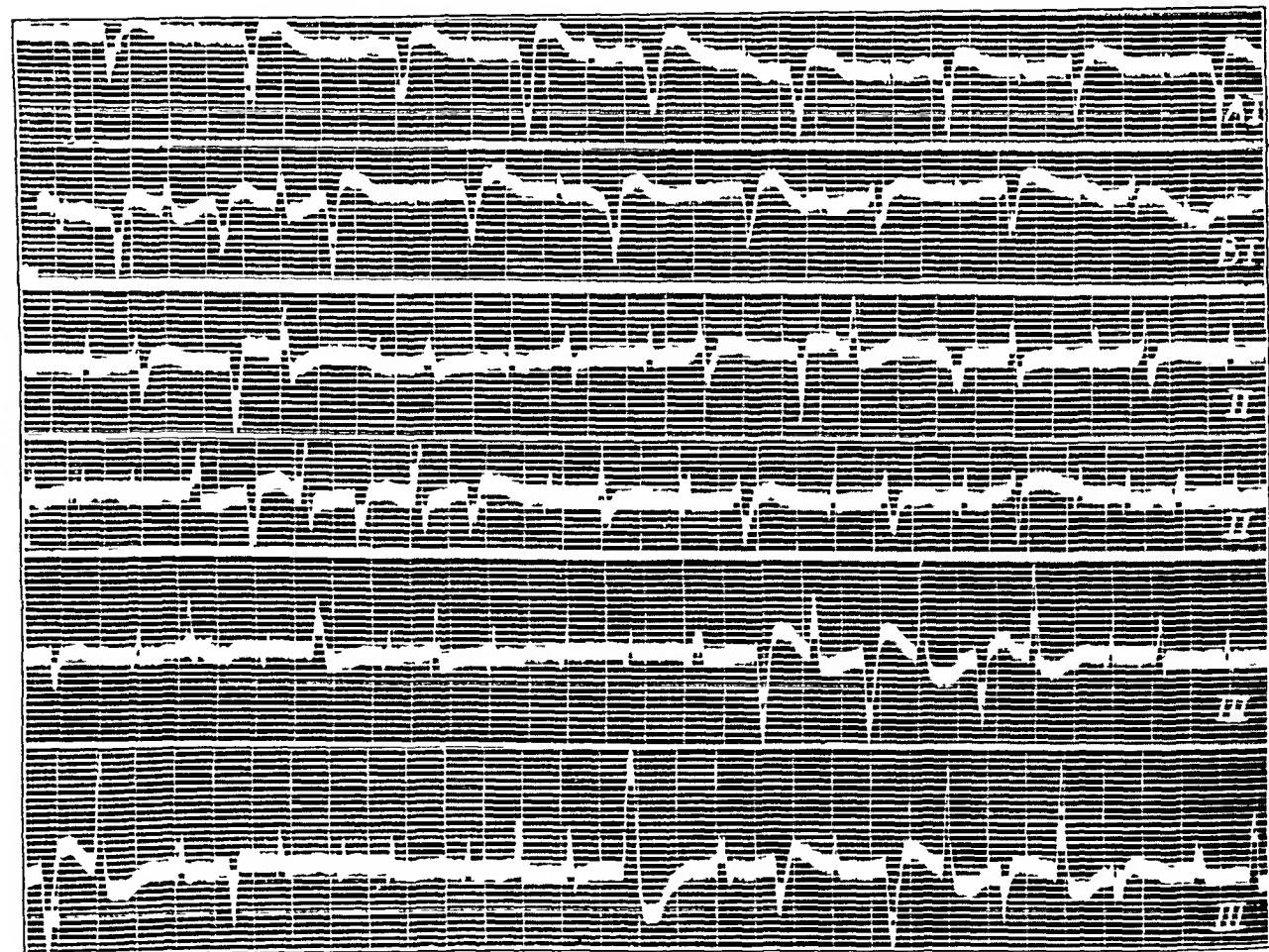


Fig 5 (Case 2) —February 10, 9 a m, first two strips, a continuous record
in Lead I, third and fourth strips, in Lead II and fifth and sixth, in Lead III

(lower part) shows a rhythmic tachycardia with alternation in the direction of the ventricular complexes. The rate is 220 a minute. This record is another example of the unusual mechanism in question.

Subsequent electrocardiograms were made at frequent intervals until the patient's death, the next morning. These show periods of the regular alternating tachycardia of varying lengths. Other portions of the curves show a mechanism which is similar but in which certain differences occur. These include the following: (a) The alternate deflections may not be invariably of opposite direction (Fig. 4, top strip), (b) The complexes, while alternating regularly in direction, may show variations in shape (Fig. 5, second, fourth and sixth strips). Other portions show bigeminy which is frequently of considerable length (Fig. 4, third strip). The space between the first and second component of the pairs is constant in places and constitutes true coupling. The

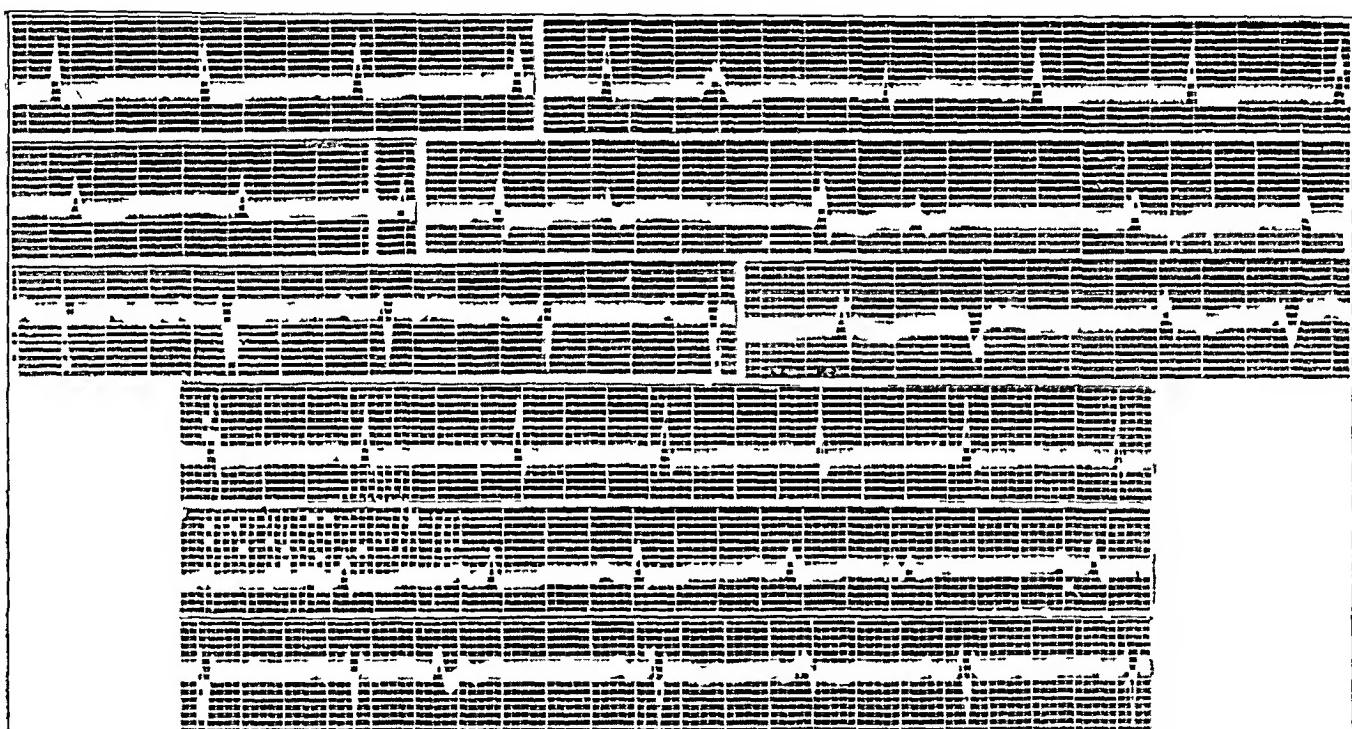


Fig. 6 (Case 3)—Upper portions of the three leads, the day of admission, Sept 13, 1920, lower the three leads at 11 30 a m, September 20, one and one-half hours before the administration of 19 cc of tincture of digitalis

shapes of both components of the couples frequently undergo considerable changes (Fig. 5, first and second strips). Still other portions of these curves show isolated couples which are quite similar to the complexes of the alternating tachycardia (Fig. 5, third strip).

CASE 3—A man, aged 71, admitted to the hospital, Sept 13, 1920, complained of dyspnea, ascites and edema of the legs. These symptoms had been present at intervals for about a year.

His general condition was "fair." There was marked edema, the liver extended 5 cm below the costal margin, the heart sounds were clear but weak. The cardiac dulness extended 17 cm to the left. There were many extrasystoles. The vital capacity was 1,700 cc. The blood pressure was 150 systolic, 100 diastolic. The urine contained a large amount of albumin and many hyaline casts. The nonprotein blood nitrogen was 44.4 mg per hundred cubic centimeters. The patient's weight was 148 pounds (67.1 kg).

There was no notation as to whether he had or had not recently received digitalis, but the history states that "heart medicine" had "relieved edema and ascites in the past." The following summary is taken from the history. The patient was kept quiet in bed with morphin and atropin or codein for the first five days without much reduction of the edema. The size of the calf of the leg was reduced from 35 to 33 cm. The signs of hydrothorax became more pronounced. The weight dropped only 22 kg. On the fifth day, he was given 0.3 gm of theophyllin every three hours for three doses. This produced no result, the patient gaining 1 kg in one day.

On the seventh day after admission, the patient was given a massive dose of digitalis (19 cc of tincture of digitalis). One and a half hours later, he showed pulsus alternans.⁶ Three and one half hours after administration, the

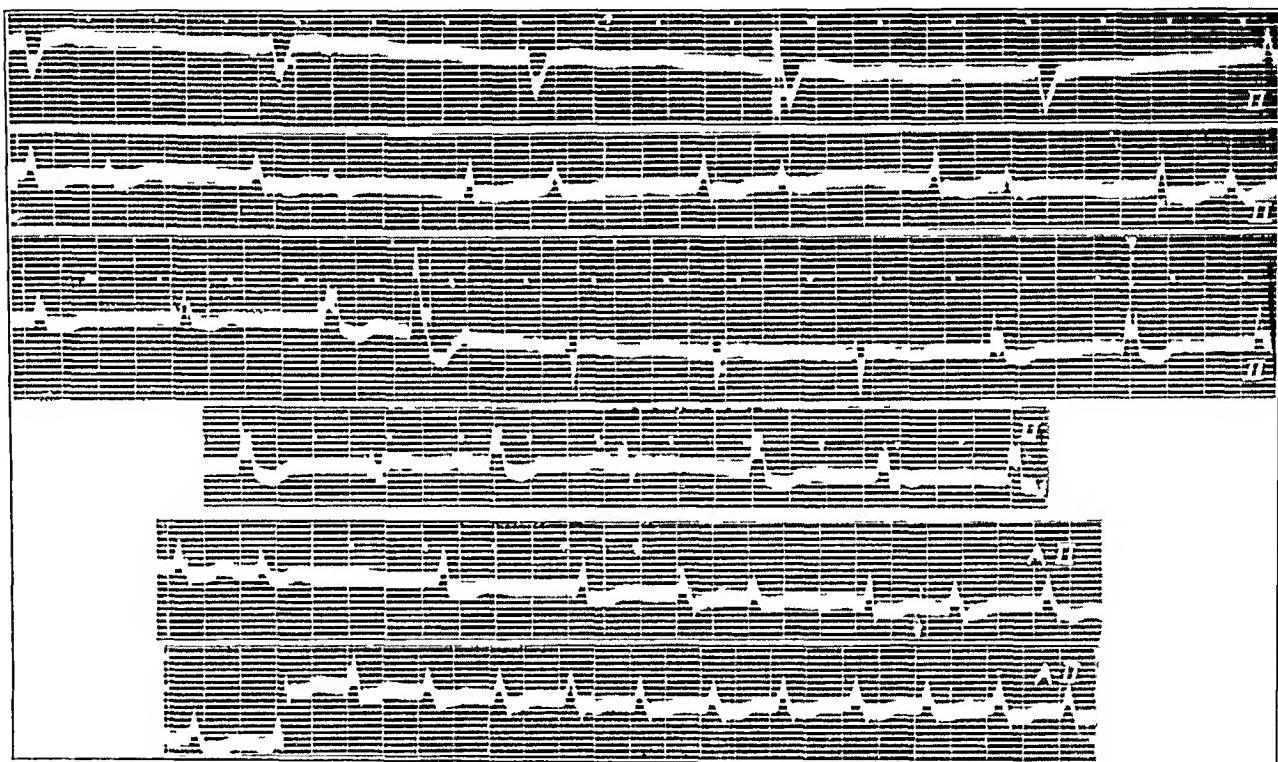


Fig. 7 (Case 3) —September 20, 4 p m, three hours after the administration of 19 cc of tincture of digitalis, all strips in Lead II, the last two strips constituting a continuous record. The position of the P waves is indicated by markers.

patient's heart went into tachycardia, rate 160. The tachycardia persisted, with the rate dropping to 130, until the patient died suddenly, five hours after the administration of a massive dose of digitalis.

The necropsy report stated that the heart weighed 600 gm (free of blood). There were ecchymotic spots along the left descending coronary branch, also, a few pericardial hemorrhages over the epicardium of the left ventricle, very few over the right ventricle. Considerable coronary sclerosis was present. The diagnosis was chronic diffuse nephritis (contracted kidney), arteriosclerosis, general, hypertrophy and dilatation of the heart, and subepicardial hemorrhages.

⁶ There is nothing in the record to show that the diagnosis of pulsus alternans was verified.

Electrocardiograms were made as follows (a) one day after admission, (b) seven days after admission, one and one half hours before the administration of the massive dose of 19 c.c. of tincture of digitalis, and (c) three hours after the administration of the digitalis.

Figure 6 (upper part) shows portions of the record made on the day after admission. The three leads are shown. The right hand part of the figure shows frequent extrasystoles which, in places, produce a bigeminy. The left hand part of the figure shows portions of the record in which extrasystoles do not occur. In the record made seven days later (Fig. 6, lower part) extrasystoles occur less frequently.

Figures 7 and 8 show portions of the record obtained three hours after the administration of the dose of 19 c.c. of tincture of digitalis. All the curves shown in Figure 7 were taken in Lead II. The first strip of this figure shows an auricular rate of 150 a minute with an independent ventricular rate of 43. The type of the ventricular complexes is different from that previously recorded. The auricular waves are quite small, a change which frequently occurs after

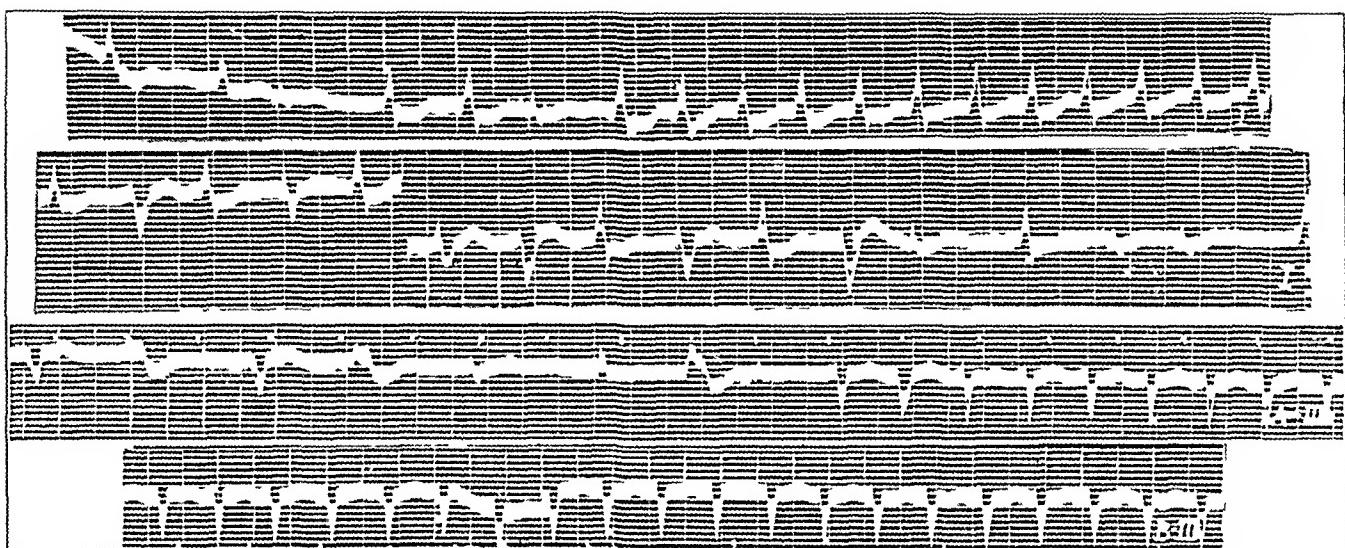


Fig. 8 (Case 3)—September 20, 4 p. m., three hours after the administration of 19 c.c. of tincture of digitalis, first and second strips, portions of Lead I, third and fourth strips, a continuous record in Lead III. The probable positions of the P waves are indicated by markers.

digitalization. Their position is indicated by markers. The second strip shows a pairing of the ventricular complexes, the shapes of both components of the pairs being similar to those which were seen the day after admission. The pairing, however, is more persistent in Figure 7, and the ventricular rate is faster. The third strip shows the auricular rate still about 150. The predominant ventricular rate is 80. In this and in the fourth strip, the shape of the ventricular complexes undergoes many changes.

The fifth and sixth strips are continuous. The latter part shows a tachycardia whose ventricular rate is 150. The beginning of this tachycardia (fifth strip) is marked by an irregularity, the exact type of which is somewhat open to question. The fact, however, that the rate of the paroxysm, after it is established, is that of the usual auricular rate, i. e., 150, would indicate its auricular origin. Auricular waves, however, cannot be clearly distinguished either in this paroxysm or in that part of the record which immediately precedes it.

Other records of tachycardia are shown in Figure 8. The first and second strips are from Lead I. The third and fourth strips constitute a continuous

record from Lead III. The first strip shows the onset of a paroxysm. The auricular mechanism is difficult to determine in this portion of the record. The rate of the ventricular complexes is 180 a minute. This is about the same as the rate at the beginning of the paroxysm whose onset is shown in the third strip, and which is probably ventricular in origin. The rate of the last mentioned paroxysm, after it is well established, is 200 a minute.

The record immediately preceding the onset of the latter paroxysm is of great interest. The small auricular complexes can be distinguished occurring at the rate that has been noted in other portions of the record, i.e., 150 a minute. The first five ventricular complexes exhibit an alternation in the direction of deflection and are of the general types indicative of interference with conduction through the right and left bundle branches. The tendency to pairing, however, would suggest that the second and fourth complexes are produced by extrasystoles which arise in the right ventricle.

A similar difficulty arises in the attempt to interpret the second strip. The complexes in this show, for the most part, an alternation in the direction of deflection. This portion of the record is quite similar to the record in the first of Schwensen's cases. The auricular mechanism in Schwensen's case, however, was normal, while the auricular mechanism in the second strip of Figure 8 is somewhat open to question. There are, however, what look like traces of small P waves occurring at the rate of about 150. The time interval between the ventricular complexes is not constant. The total rate of the ventricle for the first two thirds of this strip is 137.

One interpretation of this record that suggests itself is that the upwardly deflected complexes are premature contractions whose point of origin is in the left ventricle. In favor of this explanation is the fact that the paroxysm in the first strip is composed of complexes of similar shape, and also that the time interval between one of these beats and the beat immediately preceding it is of shorter length than the interval following it. Under this interpretation, the downwardly deflected complexes are either the "normal" ventricular beats or they also are extrasystoles. If the former, they are suggestive of delayed conduction through the left bundle branch; if the latter, they arise in the right ventricle. Another suggested explanation of these complexes is that they record a paroxysm of tachycardia whose point of origin is in the bundle at or just above its bifurcation, conduction being delayed alternately through the right and left branches. A complete explanation of these complexes is difficult to reach, but occurring as they do in close association with other mechanisms which are known to result from digitalis, the conclusion that they also are due to its action would appear clearly indicated.

COMMENT

The tachycardia which is the especial subject of this study, and which is recorded in Cases 1 and 2, presents certain features which differentiate it from that just described. It occurred in both instances, as well as in the published cases to which reference has been made in the presence of auricular fibrillation. It is rhythmic. In the case in which a number of records were obtained (Case 2), it is closely associated with accurate coupling. This association demands special comment. No adequate explanation of coupling has been reached, but it is well known that the best examples of it occur in patients with auricular fibrillation under full digitalis therapy. Lewis suggests that coupling may be

caused by reentrant beats, and he and his co-workers⁷ mention the possibility that instances in which a rapid and almost regular rhythm seems to emanate from the ventricle also may be due to reentrant beats. The most beautiful examples of digitalis coupling show an alternation in the direction of the complexes that constitute the couple, and these complexes, furthermore, exhibit, in general, shapes that are characteristic of defective conduction first through one branch of the atrioventricular bundle and then through the other.

It is frequently impossible to determine whether abnormal ventricular complexes represent aberrant beats or extraventricular systoles. Variations in the shape of ventricular complexes may be due either to changing intraventricular conduction or to changes in the points of origin of the beats. In cases that exhibit independent ventricular rhythm, the difficulty in determining which of these factors is responsible for changes in the ventricular complexes is enhanced. An explanation of the alternating tachycardia shown in these cases and in the cases reported by Schwensen, by Felberbaum and by Reid, which rests on either of the foregoing possibilities, therefore, must at present be open to question. Certain facts, however, suggest that an alternate variation in conduction through some portion of the right and left branches of the atrioventricular bundle rather than the occurrence of extrasystoles at multiple foci is responsible for the alternation in direction of the ventricular complexes of this tachycardia. The *exact rhythmicity of the complexes would be difficult to explain except on the basis of their origin at only one focus*. On the other hand, there is abundant evidence that digitalis does prolong conduction through the bundle branches as well as through the main stem. In one of my cases² which showed, as a toxic effect of digitalis, auricular tachycardia and aberrant ventricular complexes, there were short portions of the curve which showed an alternation in the direction of the aberrant complexes associated with shapes of the latter that were indicative of defect in conduction first through one branch and then through the other.

If, however, this unusual mechanism is indeed due to alternate interference with conduction through the bundle branches, it might appear that this interference, if high in the branches, must cause, not a mere delay in the conduction of impulses, but an absolute blocking of them. Otherwise, it would be difficult to explain how that branch which had just experienced difficulty in conducting an impulse could recover in time to transmit the succeeding impulse with even more facility than the opposite branch which had just showed no evidence of impairment.

⁷ Lewis, T., Druy, A. N., Wedd, A. M., and Iliescu, C. C. Observations Upon the Action of Certain Drugs Upon Fibrillation of the Auricles, Heart 9 207 (April) 1922

But these complexes do not exhibit the exact shapes that are usually attributed to complete bundle branch block. A possible escape from the dilemma is suggested in a recent report by Carter and Dieuaide⁸ of the recurrence of complete atrioventricular block in a patient who showed normal atrioventricular conduction between attacks. These authors suggest that there is normally a large reserve in the conducting capacity of the atrioventricular bundle, and that a few fibers may transmit impulses without delay even though the bulk of the bundle may have suffered serious impairment. If this is true of the main stem, it may apply also to the bundle branches. Under this conception, the alternating tachycardia might be explained as follows. Digitalis intoxication results in a tachycardia which originates at or near the bifurcation of the main stem of the bundle. The action of the drug has also impaired to a considerable extent the conductivity of the bundle branches. An impulse is then transmitted over one (the right) branch but finds the other (the left), for the most part, unable, at the moment, to transmit it. A small strand in the impaired left branch, however, does transmit the impulse, but at a slower rate. This gives the picture of defective (left) branch conduction. The next rhythmic impulse finds the bulk of the left branch restored and ready for conduction, but the bulk of the right branch has not recovered, and so fails to transmit the impulse. A small strand in the right branch, however, having been less impaired by digitalis, is able to transmit the impulse but at reduced speed. This produces the picture of defective right branch conduction. The bulk of the tissues of the right branch is then ready for the succeeding beat, but the main part of the left branch is not, and so on with successive rhythmic impulses.

The question cannot be settled merely by an inspection of records. It would, perhaps, be impossible to say whether the complexes in the latter part of the last strip of Figure 5 are aberrant, or whether they represent impulses which arise at different foci. The sixth and seventh complexes from the end alternate in direction and are fairly typical of those composing the long, regular paroxysms. On both sides of this pair the complexes change in shape. There is little to strengthen either interpretation of the cause of these changes. Digitalis is known to produce extrasystoles. It is known to increase rhythmicity². It is also known to depress intraventricular conduction⁷. Both extrasystoles and aberrant complexes, doubtless, occur in many cases of severe digitalis intoxication, and it is in just such cases that independent ventricular tachycardias occur⁹.

⁸ Carter, E. P., and Dieuaide, F. R. Recurrent Complete Heart Block with Normal Conduction Between Attacks, Bull Johns Hopkins Hosp 34 401 (Dec.) 1923

⁹ Luten (Footnote 2) Schwensen (Footnote 3) Reid (Footnote 5)

The alternating tachycardia in question may be the expression of some sort of circulating mechanism in the ventricle. And just as the speed of transmission of impulses and the duration of the refractory phase may influence the type of circus movement in the auricle, so it may be that these factors cause further changes in such a ventricular mechanism and that, in this manner, ventricular fibrillation is produced. Experimental studies along these lines may explain the mechanism by which digitalis produces this peculiar tachycardia and by which it may possibly be shown that the latter ends in ventricular fibrillation. When the exact nature of digitalis coupling is explained, it seems probable that the key to the explanation of this alternating tachycardia will have been found.

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THE PATHOGENESIS OF TETANY

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Tetany may be defined as a condition of peripheral nervous hyper-excitability, characterized by intermittent spasms of the extremities, without loss of consciousness

The first reference in the literature to tetany is attributed to Clarke (1815) Other names, particularly those of Kellie, Steinheim and Dansie, are associated with the earlier descriptions of the condition The title "tetany" we owe to Corvisart

Tetany can scarcely be regarded as a distinct clinical disease but rather as a syndrome which may occur under a number of widely differing circumstances A proper understanding of the nature of this syndrome necessitates a close examination of the various etiologic conditions Lacking a more accurate classification, the tetanies are usually studied under one of the following divisions

- 1 Tetania parathyreopriva
 - 2 Traumatic tetany
 - 3 The idiopathic tetany of workmen
 - 4 The tetany of gastro-intestinal disorders
 - 5 Infantile tetany or spasmophilia
 - 6 Maternity tetany
 - 7 Guanidin tetany
 - 8 The tetany of forced respiration
 - 9 The tetany of nervous diseases
 - 10 The tetany of alkalosis and acidosis
 - 11 The tetany of intoxications, infections, and "overexertion"
- Each of these varieties demands closer examination

1 TETANIA PARATHYREOPRIVA

This is due to removal of the parathyroid glands This class also includes the cases of so-called tetania strumipriva, or the tetany complicating goiter operations

The earlier thyroid surgeons (Schiff, Wagner, Colzi, Sanquirico, and Canalis, Horsley, Weiss, Kocher, Billroth, Reverdin and v Eiselsberg) were perfectly familiar with the train of convulsive symptoms which often followed the complete removal of goiter, although they did not appreciate its significance The existence of the internal parathyroids had been recognized by anatomists since their discovery by Sandstrom in 1880, but it was not until Nicolas, in 1893, had described the second or external pair of parathyroids that experiments in animal removal were seriously undertaken Roux (1897) and Vassale and

Generali (1900) were among the first to extirpate all four parathyroids, and in the great majority of cases the animals died with the convulsive manifestations known to the thyroid surgeons as tetany. Necropsy revealed no evidence of sepsis, hemorrhage or undue trauma. Further experiments were performed by Biedl, Leischner, Lusena, Cristiani, Alquier, Welsh, Edmunds, Gozzi and many others, all demonstrating clearly the association of the resulting symptoms with the tetany that had been observed to follow goiter operations. The postoperative results were not entirely uniform however, although the majority of animals died as a result of parathyroidectomy, nevertheless there were survivors. It was gradually realized that certain other factors influenced the severity of the symptoms.

Age—Young animals were found to be more susceptible to the effects of parathyroidectomy than adults (Berkeley and Beebe, Marine, Simpson)

Type of Animal—Carnivora most readily developed tetany, herbivora least of all. Omnivora occupied an intermediate position.

Pregnancy—The operation results were severest in pregnant animals (Morse, Carlson)

Heredity—The offspring of parathyroidectomized animals were particularly susceptible (McCarrison)

Diet—Feeding on flesh or meat extracts usually aggravated the symptoms, whilst the tetany could sometimes be kept in abeyance by a milk diet (Berkeley and Beebe, Marine, Morse, Paton and Findlay). Dragstedt, Phillips and Sudan (1923) find that feeding with putrid meat produced more violent manifestation than a fresh meat diet.

Coexistence of Rickets—Rachitic animals are very susceptible to parathyroidectomy (Morel, Paton and Findlay). Animals that survived the acute phase passed into a state of "latent tetany" characterized by emaciation, weakness and numerous trophic disturbances such as falling out of the hair, osteoporosis, enamel changes and cataract formation. Acute convulsive manifestations were readily precipitated by even the slightest stimuli, such as the advent of pregnancy or the estrum, the injection of tuberculin or of placental extract.

2 TRAUMATIC TETANY

This group comprises those cases of tetany where actual damage to the parathyroid glands has been known to occur. Thus Cordier reported fatal tetany in a man, aged 41, necropsy demonstrated a large cervical hematoma which had destroyed all the available parathyroid tissue. Proescher and Diller have recorded fatal tetany occurring in a young man eight days after a severe blow. Postmortem examination revealed numerous recent hemorrhages into the parathyroids, which

appeared to be hypoplastic. Cases of sudden death among infants occasionally occur as the result of traumatic hemorrhage into the parathyroids. Three such cases have been recorded by Crosser.

3 IDIOPATHIC TETANY

This is the name applied to a particular form of tetany, rare in this country but not uncommon in certain parts of the continent. It also goes under the names of tetany of workmen, or epidemic endemic tetany.

Etiology.—There are many points of very great interest in the etiology of this condition.

Sex. Men are much more often affected than women. Out of 418 cases collected by v Frankl-Hochwart, 399 occurred in men and only nineteen in women.

The age incidence is that of early adult life (from 15 to 25).

Place. Tetany is endemic in Vienna and Heidelberg, but becomes epidemic in character about every tenth year. The other parts of Austria and Germany are comparatively free from the disease. Tetany occurs also in Russia and other parts of the Continent but is rare in Great Britain and America. In India, tetany is endemic in certain valleys in the northern provinces, often corresponding with the goiter districts.

Heredity appears to contribute to the production of tetany, and several members of a family may be simultaneously attacked.

Occupation, for some obscure reason, constitutes an important etiologic factor. A large proportion of the men affected are tailors and shoemakers by trade, whilst among the women, seamstresses are most frequently affected. Out of 528 cases collected by v Frankl-Hochwart, 223 were shoemakers and 117 were tailors. In the Petrograd outbreaks of tetany, metalworkers are particularly liable to the disease (Voss).

Seasonal incidence. A very large percentage of the cases occur in the spring, February, March and April being sometimes spoken of as "the tetany months."

The prognosis is good in these cases, the average length of the illness being from two to three weeks. Death is extremely rare.

4 THE TETANY OF GASTRO INTESTINAL DISORDERS

There are two main varieties of alimentary disorders which are apt to be complicated by tetany: (1) gastric dilatation, (2) colonic inflammations (chronic diarrhea, worms, etc.).

Gastric Tetany.—The commonest etiologic factors in this condition are persistent vomiting and dilatation of the stomach.

Tetany is a rare complication in gastric diseases and probably never occurs except in patients who were in a state of latent tetany. In such persons, acute symptoms are brought on by quite trivial stimuli, thus

they may arise during the operation of gastric lavage or even after simple percussion over the epigastrium (Gerhardt)

During infancy, gastric tetany occasionally arises in the course of such diseases as cyclic vomiting, congenital duodenal stricture, or hypertrophic stenosis of the pylorus

Experiments were made by MacCullum, Lintz, Vermilye, Leggett and Boas on the operative occlusion of the pylorus in dogs. Tetany appeared after a variable interval. There was an increase in the alkali reserve of the blood. The experiments were repeated the following year by Hastings, Murray and Murray, with the production of tetany in every case. The blood showed an increase both in the alkali reserve and in the calcium content.

Colonic Tetany.—This is usually preceded by a prolonged spell of diarrhea. In adults, tetany has been reported as a complication in such diseases as sprue (Bassett-Smith, Dorvain, Barach, and Murray) or chronic dysentery (Savy and Langeron). Blumgart reports two cases of chronic diarrhea, anemia, and acidosis, in which tetany was a terminal feature. Tetany may also occur in infections with a tapeworm (Riegel, Greenfield).

In infants, celiac disease or tuberculosis of the bowel occasionally give rise to tetany. Langmead (from 1906 to 1909) collected nine cases of tetany in children, aged from 2½ to 8 years, associated with dilated colon, chronic diarrhea, and the passage of offensive, porridge-like stools. Possibly these were actually cases of celiac disease.

5 INFANTILE TETANY (SPASMOPHILIA)

During the first three years of life many infants are characterized by hyperexcitability of the peripheral nervous system and by muscular hypertonus. From time to time these children may be seized with generalized convulsions or attacks of laryngeal spasm. Such children were spoken of by Finkelstein as exhibiting the "spasmophil diathesis." Occasionally attacks occur which are indistinguishable from those of adult tetany. Such attacks usually show a definite seasonal incidence, and are closely associated with rickets and gastro-intestinal disorders.

In studying a series of cases of infantile tetany, two main groups may be detected:

(a) A larger group of cases almost always occurring in improperly fed infants. Rickets is very frequently present, and the tetany is usually preceded by an attack of gastro-enteritis. (b) Cases of tetany of other causation, occurring in infants. Such instances are those of nephritis tetany, the tetany of chronic diarrhea, etc. The children are usually a little older, and there is no definite etiologic association with rickets. These cases form but a small group and should be considered apart.

Male infants with tetany slightly outnumber the female, and the poorer classes are more often affected than the well-to-do. There is a definite seasonal incidence, the majority of all cases occurring in the months of February, March and April. Scarcely any cases are met with during the summer months. Dr John Thomson remarked on the prevalence of tetany when cold winds were blowing.

Heredity certainly takes a part in the etiology, the mothers of many spasmophilic infants themselves show signs suggesting a condition of latent tetany.

Inquiry into the diet elicits many points of interest:

1 Tetany is very rare in breast-fed infants.

2 Tetany usually arises in babies fed on one of the proprietary milk preparations, less frequently it is seen in infants fed on cow's milk mixtures. Finkelstein set out to determine which constituent of milk was responsible for the production of tetany. By the addition of the various components of milk to the dietary he found that neither the fat, sugar nor protein was responsible, but that one or all of the inorganic salts was the causative factor. Brown and Fletcher found that infants fed on a high carbohydrate dietary were liable to develop tetany, provided the proprietary article had been subjected to a high temperature in the course of its manufacture.

The association of rickets with tetany is particularly striking, being first pointed out by Sir William Jenner. In Kirchgasser's series of 263 cases, rickets was present in 79.8 per cent. Escherich puts the proportion as high as 95 per cent. Associated with attacks of tetany, laryngospasm or even generalized convulsions may occur simultaneously. The actual precipitating cause of tetany in rachitic children is usually an attack of gastro-enteritis. Acute specific fevers, bronchopneumonia, streptococcal sore throats, teething or worms will also act as a source of irritation sufficient to translate latent spasmophilia into actual tetany.

6 MATERNITY TETANY

Tetany may arise in the course of pregnancy (tetania gravidarum) or during lactation (tetania lactarium). It is uncommon in this country, but is not rare in Vienna and other localities where tetany is endemic. The patient during the latter half of pregnancy is much more liable to tetany, especially during the sixth, seventh and eighth months. The actual onset may even date from the commencement of uterine contractions (Neumann).

7 GUANIDIN TETANY

Guanidin is a nitrogenous basic substance of highly toxic properties, occurring in minute traces in the liver, muscles, serum and urine, and is probably excreted either as creatinin or urea. Convulsive manifestations have been known to follow injection of the substance (Gergens and Baumann, 1876, Pitzey and Swaen, 1876, Fuhner, 1906).

Paton and Findlay (1916) carried out a series of injection experiments in animals, with the production in every case of symptoms indistinguishable from those of parathyroid tetany. One may reproduce here a summary of their findings:

1 Small doses of guanidin excite the spinal cord while large doses depress it

2 Guanidin tetany is relieved by calcium

3 Latent tetany can be precipitated by guanidin in doses insufficient to cause symptoms in normal dogs

4 Guanidin increases the electrical excitability of the peripheral nerves

5 There is an optimum concentration for the action on the peripheral nerves, while the action on the central nervous system is directly proportional to the dose

6 Parathyroid tetany resembles guanidin tetany in all particulars (spasticity, tremors, increased electrical excitability, loss of balance, etc.)

8 TETANY OF FORCED RESPIRATION

Tetany arising in the course of alterations in the respiratory rhythm (light anesthesia, tachypnea, etc.) has been noted by Vernon (1909), Yandell Henderson (1909), Hill and Flack (1910), Stein (1916) and Collip and Backus (1920). Barker and Sprunt (1921) reported a case of hysterical polypnea followed by tetany occurring as a sequel to encephalitis lethargica. The most interesting contribution, however, has come from America, Grant and Goldman (1920) produced transitory attacks of tetany in normal persons by the process of "over-ventilation of the lungs." The subject, lying on his back, breathed as deeply as possible, slowly and regularly. In every case, tetany developed after an interval of from fifteen minutes to an hour.

9 THE TETANY OF ALKALOSIS

There are many cases on record of tetany arising after the therapeutic administration of large doses of alkalies. Blum produced spasms in diabetic patients by the intravenous administration of alkalies. Howland and Marriott recorded other cases among infants. Horrop produced tetany in an adult with mercurial poisoning by the administration of bicarbonate of soda. Healy recorded six instances of tetany developing in women after the rectal administration of 80 gm of sodium bicarbonate in mistake for simple enemas. Four of the patients died but the other two recovered after vigorous calcium medication. Another case of tetany in alkalosis is reported by Tiletson and Underhill.

10 THE TETANY OF ACIDOSIS

Although cases of actual tetany are rare manifestations in acidosis, an increase in the electrical excitability of peripheral nerves is not

uncommon in bronchopneumonia, pertussis, nephritis, rickets and other diseases of infancy associated with an alkaliopenia. It is possible that the tetany which has been observed to follow the administration of serum is actually an example of the tetany of acidosis.

11 THE TETANY OF NERVOUS DISEASES

Tetany has been observed as a rare complication in certain nervous disorders, in particular, cerebellopontine angle tumors, syringomyelia, meningitis and Friedreich's ataxia.

12 THE TETANY OF INFECTIONS AND INTOXICATIONS

Occasionally tetany arises in the course of an acute specific fever, especially in those districts where idiopathic tetany is endemic. Typhoid in particular is apt to be complicated by tetany, while it is not unknown in the course of influenza, pneumonia, scarlet fever or cholera. The various intoxications, lead, mercury, chloroform, alcohol, morphin, male fern, spermin, and phosphorus have all been known to give rise to tetany.

13 THE TETANY OF OVEREXERTION

James Collier has recorded a case of a girl guide who constantly developed typical tetanic spasms after she had performed long distance marches.

CLINICAL FEATURES OF TETANY

With a few relatively unimportant exceptions, the symptomatology of the various types of tetany is remarkably similar. A brief description is advisable of the phenomena common to these varieties. The brunt of the morbid process falls on the nervous system, the peripheral neurones suffering more than the higher centers. The phenomena may be conveniently studied under three headings (1) motor, (2) sensory, (3) sympathetic or vasomotor.

The chief motor manifestations consist of intermittent tonic spasms of the extremities, without any loss of consciousness. The hands and feet take up characteristic postures (accoucheur's hand, carpopedal spasm). In animals there are in addition muscle fibrillation, hypertonus, choreiform macrokinetic movements of the limbs, and "intention spasms." The peripheral nerves are markedly hyperexcitable and respond with the greatest readiness to mechanical and electrical stimuli.

Sensory manifestations are rarer and include subjective sensations of pain, numbness, tingling, etc. There may be an actual electrical hyperexcitability of the sensory nerves (Hoffmann) or the nerves of special sense (Chvostek, Jr.). Kashida has pointed out that the application of hot or cold objects may elicit an increased sensory motor reaction.

Sympathetic upset is expressed by involvement of the unstriped musculature and by vasomotor derangements. Thus one may find spasm of the esophagus and larynx and of the pyloric, anal or pupillary

sphincters, of the diaphragm (Bechterew), or of the bronchi. Alterations may occur in the respiratory mechanism causing apnea or polypnea. Tachycardia is common, especially in dogs, and death has been said to occur from "tetany of the heart." Among the vasomotor upsets one may include lachrymation, polyuria, salivation, intermittent hydrathroes, edema, mydriasis, hyperhidrosis and dermographism. Arterial spasms may give rise to a condition resembling Raynaud's disease, or even to transient attacks of amaurosis. Falta states that there is an increased susceptibility to injections of pilocarpin and epinephrin.

METABOLISM IN TETANY

All clinical varieties of tetany are accompanied by grave metabolic changes which, although differing in certain details, present on the whole a marked uniformity. The most constant and striking alterations in the majority of cases of tetany occur in the calcium metabolism. There is first an increased excretion of lime and a reduction in the urinary calcium/fecal calcium ratio. Secondly there is a depletion in the calcium reserve of the body. Edheim remarked on enamel changes rapidly following parathyroidectomy, causing the teeth to decay and snap off, fractures also healed slowly and with imperfect callus. Leopold and v Reuss found a quantitative diminution in the lime content of the bones, whilst Iselin reported osteoporotic skeletal changes. The proportion of lime falls in muscles (Underhill and Blatherwick) and also in the brain (MacCullum and Voegtlín, Edmunds, Quest and Czerny). A reduction in the serum calcium content is a very frequent phenomenon, Howland and Marriott maintain that tetany will not arise until the calcium level falls from the normal (10 mg per cent) to 5 mg. Cruickshank (1923) states that there is a relative increase in the amount of diffusible calcium, with a reduction in the total quantity. The amount of calcium in the cerebrospinal fluid is normally very constant, but in tetany it may be reduced to mere traces (Critchley and O'Flynn). Although the reduction in the serum calcium content is usual, there may, however, be actually a slight increase in certain varieties of experimental tetany (e.g., after forced respiration, or the ligation of the pylorus in dogs). The whole picture of the calcium metabolism may be crystallized in the term "negative calcium balance."

Changes may occur in the metabolism of other inorganic compounds, thus a phosphorus retention is common (Greenwald, Salvesen), sodium and potassium are often retained and the excretion of sulphur may be increased (Greenwald). Changes in the magnesium content are not constant (Howland and Marriott). Loeb and Matthews emphasize the importance of the balance between the metallic salts in

tetany, in their opinion the characteristic change lies in the increase in the ratio $\frac{\text{sodium} + \text{potassium}}{\text{calcium} + \text{magnesium}}$ in the blood (Kramer, Tisdall and Howland)

The nature of the acid base upset in tetany is controversial, as both acidosis and alkalosis have been observed. In tetania parathyreopriva, Morse, Cordier, Togawa, Salvesen and Greenwald have reported states of acidosis, whilst McCann stated that an alkalosis is present. Wilson, Stearns and Thurlow state that there is a condition of alkalosis rapidly followed by acidosis. Howland and Marriott found a normal alkali reserve. Alkalosis was constant in the tetany of forced respiration.

The nitrogen metabolism is characterized by

- 1 An increased excretion of nitrogen
- 2 An increased $\frac{\text{urea N}}{\text{total N}}$ ratio in urine
- 3 An increased ammonia ratio
- 4 An occasional rise in the ammonia content of the blood
- 5 Creatinuria and an increased output of creatinin (In guanidin tetany there is also an increase in the creatin content of the muscles [Wishart])
- 6 The appearance in the blood stream of certain protein derivatives normally excreted as urea and which are highly toxic bodies. Chief among these are guanidin and methylguanidin. The origin of these bodies is uncertain and cyanamid (Koch), arginin, creatin and lecithin (Paton) have been cited as the possible precursors. The urinary output of these bodies is also greatly increased, and there is a reduction in the amount of guanidin normally present in muscle.

There are but few references in the literature to the metabolism of the carbohydrates. Watanabe reported a lowering of the blood sugar level in experimental tetany and G A Clark has found a similar condition in guanidin tetany.

The utilization of fats by the organism appears to be diminished (Underhill, Tilestone and Bogert).

The pathogenesis of tetany is still a matter for much speculation and many theories have been formulated to explain its clinical and pathologic features. The earlier observers regarded tetany as a manifestation of acute rheumatism, later it was spoken of as a form of intermittent tetanus. Today there are three main hypotheses which demand attention, and they may be spoken of as the calcium privation theory, the endocrine theory, and the theory of toxic origin. Each one requires closer study.

THE CALCIUM PRIVATION THEORY

This theory, formulated by MacCallum and Voegtlín in 1908, has received wide recognition, being based on a large number of observations, experimental, clinical, metabolic, pathologic and therapeutic. Thus Sabbatani (1901) by applying a solution of lime salts to rabbits' convolutions, was able to reduce the excitability, conversely, the applica-

tion of calcium precipitating solutions (e.g., oxalates) caused a hyper-excitability of the cerebral cortex Loeb (1902) showed that the injection of oxalates or citrates into animals produced muscular twitchings MacCallum, Lambert and Vogel (1914) perfused an amputated limb with calcium freed blood, with the production of peripheral nervous hyperexcitability On the clinical side, tetany is known to occur frequently in conditions characterized by a calcium drain such as pregnancy, lactation, rickets and occasionally osteomalacia Biochemical examination shows that the calcium content of the serum and cerebro-spinal fluid is very frequently reduced while the output is increased, at the same time there is an actual diminution in the amount of calcium present in the brain, muscles, bones and teeth The therapeutic value of intravenous calcium salts in tetany is unquestionable although the effect wears off after twenty-four hours Bergheim, Stewart and Hawk (1914) and Salvesen (1922) have shown that the manifestations of tetania parathyreopriva may be kept in abeyance by feeding the animals on a high calcium diet for some time before operation

These observations are all of striking interest and merit close consideration, but a number of opposing facts may be cited which combine to render this present theory untenable Thus whilst conditions of increased lime excretion are undoubtedly liable to be followed by tetany, nevertheless tetany even more frequently occurs without any such etiologic factor being demonstrable Secondly, the interpretation of the results of blood calcium analyses requires consideration, can the low figure in tetany be due to a mere mechanical dilution of the blood by a condition of hydremic plethora, as in some cases of nephritis? Or again, may not the low calcium figure be the result rather than the cause of the tetany? Thus in cases of rapidly produced experimental tetany (as in forced respiration or ligation of the pylorus) there is no reduction in the serum calcium Moreover, in diabetes and other diseases the calcium level may fall considerably without tetany resulting The figures may also be lowered experimentally by the injection of phosphates, or copious bleeding followed by saline infusions, and no tetany appears With reference to the benefit from calcium medication, it must be remembered that calcium is not alone in its therapeutic effect, thus barium and magnesium salts are also efficacious, Canestro has derived benefit from injecting strontium compounds, whilst Frouin found lanthanum and thorium of value Saline transfusions may also be beneficial (MacCallum and Voegtl, Joseph and Meltzer) Most important of all, Paton and Findlay, Cruickshank and many others have shown that mere bloodletting alone will definitely improve symptoms in tetany

THE PARATHYROID THEORY OF TETANY

The striking similarity in clinical and metabolic features of the tetanies to the manifestations following parathyroid removal tempt one

to formulate a common pathogenesis. The unitary conception of Pineles' attempts to place all varieties of tetany on a common pathologic basis, namely, parathyroid insufficiency. Thus the idiopathic tetany of Vienna is said to be due to an acute specific infection picking out the parathyroid glands, gastric and colonic tetany arise from the action of bowel toxins on an unstable parathyroid system, maternity tetany is due to a physiologic parathyroid upset aggravated by a severe calcium drain, spasmodophilia is due to a lesion of the glands in infancy and Erdheim and others have found hemorrhages into the glands at necropsy, guanidin tetany is due to lack of the ferment arginase, which is present in the parathyroids and which converts guanidin into urea.

This hypothesis, however, is deplorably barren in chemical, histologic or clinical evidence. The significance of necropsy parathyroid hemorrhages is very doubtful, they are commonly found in postmortem examination of patients dying in convulsive or comatose states, such as cerebral tumor, uremia, etc. Moreover, histologic evidence has been negative in the great majority of necropsies on cases of tetany. The hypothesis of the toxic action of bowel amines in the production of gastric and colonic tetany is unsupported by the work of Muller, Strauss, Gumprecht, Ewald and Jacobsohn, Albu and others, who have searched in vain for any such poisonous bodies. Tetany, however, is conspicuously rare in those cases which are essentially characterized by fecal stasis and toxin absorption, namely, Hirschsprung's disease, splanchnoptosis, and chronic intestinal obstruction.

The evidence of parathyroid instability during pregnancy is extremely meager, and there are many other gross metabolic changes apart from those occurring in the calcium balance. It seems extremely improbable that the absence of four such minute bodies as the parathyroids should deplete the organism of its supply of arginase when the spleen is known to contain large amounts of this ferment. The tetany of forced respiration is scarcely explicable by this theory, for it is difficult to conceive a temporary parathyroid insufficiency occurring in a normal person and persisting only for an hour. Lastly, it may be pointed out that although parathyroid grafting is occasionally of value in the tetany following goiter operations, the treatment of tetany by parathyroid extract is futile.

THE THYROIDAL THEORY

In many respects the thyroid and parathyroid glands are opposed in function, and it is conceivable therefore that the symptoms of parathyroid tetany may be due to an uncompensated thyroidal effect (Rudinger). McCarrison has shown that the geographic distribution of idiopathic tetany corresponds closely with that of endemic goiter. Such an hypothesis, however, fails to explain why tetany should occur

when both thyroid and parathyroids are simultaneously removed. The clinical expression of thyroid overactivity, namely, exophthalmic goiter, bears but little resemblance to tetany parathyreopriva.

THE THEORY OF THYMUS OVERACTIVITY

Uhlenhuth (1917) injected salamander larvae with thymic extract and so produced tetany. At a later stage in their development, namely, after the appearance of the parathyroids, spontaneous cure resulted. Uhlenhuth thereupon suggested that the thymus and the parathyroids had mutually opposing secretions, the tetany following the removal of the latter was therefore due to the uncompensated action of the thymus.

On the other hand, Honeyman has shown that removal of the thymus and parathyroids, in mammals at least, will result in tetany. Moreover, removal of the parathyroids in the adult will still cause tetany, although the amount of active thymus tissue must be extremely small. Again, conditions giving rise to an hypertrophy of the thymus, such as may occur with lymphosarcomas, or in myasthenia gravis, are not characterized by symptoms of tetany.

THE ANOXEMIA THEORY

Morris (1923) demonstrated that the production of a state of anoxemia in animals caused a constant increase in the electrical excitability of the peripheral nerves. This artificial oxygen starvation he produced by the following methods: (a) by partial asphyxiation, (b) by lowering the surface temperature, (c) by producing a profound anemia, (d) by the administration of sublethal doses of cyanides, thus creating a nondissociable hemoglobin-oxygen combination.

In every cases, peripheral hyperexcitability (increased electrical excitability) resulted.

Clinically, conditions of anoxemia may arise in (1) profound anemias (e.g., rickets, sprue), (2) conditions of malventilation (as in the Glasgow slums where rickets and tetany are rife), (3) pulmonary diseases, where increased electrical excitability or even tetany may occur. Bronchopneumonia and whooping cough are the best examples of this type. Morris found a cathodal opening contracture of 3 m.a. in two infants with bronchopneumonia and a cathodal opening contracture of 1.8 in a case of pertussis.

Associated with these states there may be also a reduction in the serum calcium content.

Before accepting this theory it must be remembered that bronchitis is a frequent concomitant of rickets, hence probably the associated increase in nervous excitability and lowered serum calcium in respiratory diseases. The anemia in rickets and sprue is seldom so profound

as to cause an anoxemia, while tetanic manifestations are rare in the very grave anemias Incomplete oxidation is known to precipitate calcium in various situations, no such calcareous deposition occurs in tetany

THE GUANIDIN THEORY

The injection of guanidin has been known to produce muscular spasms in animals since 1876, but no association was ever suggested between these phenomena and tetany until Koch in 1912 demonstrated that methylguanidin appeared in increased amounts in the urine of parathyroidectomized dogs Burns and Sharp (1916) estimated the guanidin content of the urine and blood in normal and tetanic dogs, and found a marked increase in the latter They then found a similar increase in the urine of spasmophilic infants Paton and Findlay therefore commenced a series of experiments in the production of tetany by guanidin injection They found in every case such a striking similarity in clinical and metabolic phenomena that they formulated the theory of guanidin intoxication as the cause of tetany The function of the parathyroids they believed lay in the regulation of guanidin metabolism and the control of muscle tonus The rôle of the calcium reserve was to render the toxins innocuous, either by direct combination or by decreasing the permeability of the tissue cells

This hypothesis, although accounting for most of the phenomena in tetany, fails, however, in some few particulars It does not explain the changes in the acid base equilibrium which are so prominent in tetany, neither does it explain the rapid production of tetany in normal persons by a process of overventilation of the lungs These are both phenomena of great importance in the pathogenesis and require explanation

PRESENT THEORY

On reviewing the facts at one's disposal concerning the etiology and metabolism of each variety of tetany, it will be noticed that only one feature is common to all, namely, an alteration of the metabolism of nitrogen Calcium upset and disorders of the acid base equilibrium are both of frequent occurrence, but there are many cases of tetany in which no such changes are demonstrable The present suggestion is that the precipitating cause in all types of tetany is an alteration in nitrogen metabolism leading to the appearance in the blood stream of highly toxic nitrogenous by-products which are normally excreted as urea or creatin These toxic substances are probably guanidin or some of its derivatives Two other factors of importance will require explanation (1) The cause of the perverted nitrogen metabolism, (2) the rôle played by calcium

The factors regulating the metabolism of nitrogen are extremely numerous and upset if any one of these is liable to give rise to tetany

Whilst the exact nature of these regulating processes is unknown, many probable factors may be pointed out

ENDOGENOUS FACTORS

Parathyroid Integrity—The gross changes in nitrogenous equilibrium resulting from parathyroid removal suggest that an important if not the principal function of these glands is to help control the metabolism of nitrogen. In the absence of adequate compensating factors, therefore, parathyroid removal is followed by abnormal katabolic changes in the nitrogen reserve, which are manifested clinically as tetany.

Autoxtoxications—Pregnancy may be regarded in many ways as a state of toxæmia in which the nitrogen balance suffers. Severe perversion will lead to tetany. The gastro-intestinal varieties of tetany are also capable of a similar explanation.

H⁺/OH⁻ Equilibrium—Gross changes in the acid base balance naturally alter the normal nitrogen functions, and in several cases tetany results. Such may be the explanation of the tetany following massive alkali medication, the tetany of ketosis, or the administration of serum, and of forced respiration.

EXOGENOUS FACTORS

Diet—It is possible that nitrogen metabolism is affected by an inadequate or unsuitable dietary or by the absorption of poisons from the alimentary tract. Examples may be found in ergotism, intoxication by the male fern, lead, mercury, spearmint, etc. A high creatin diet is another deleterious influence on the normal path of nitrogen.

Respiration—Conditions of anoxæmia or conversely a deficiency in carbon dioxide, by altering the acid base mechanism of the body, alter the ammonia reserve. This suggests an explanation for the occurrence of electrical hyperexcitability in states of partial asphyxia, and also the tetany of forced respiration.

Vitamin Deficiency—The metabolic results of a vitamin deficient diet are extremely varied and nitrogen suffices to no small extent, as may be shown by the occurrence of acidosis. Hence possibly arise the spasmophilia of rickety infants, and the tetany occurring in sprue and celiac disease. It is not even necessary for the diet to be deficient in a vitamin, the important point is the absorption. Conditions of chronic diarrhea and persistent vomiting are essentially states of malabsorption and it is conceivable that tetany, when arising in these diseases, is due primarily to nonassimilation of vitamins.

Acute Infections—The epi-endemic nature of the tetany of workmen, its hereditary and familial tendencies, its seasonal incidence, its

transient and often febrile course, the frequency of recurrences, all point to an acute organismal infection. Paton and Findlay suggest that the virus selects the parathyroids the same way that mumps picks out the parotid gland.

The rôle of the calcium metabolism lies in the neutralization of circulating toxins either by direct combination to form an innocuous substance or by rendering the tissues less permeable. The circulating calcium acts as a restraining influence on the activity of the central nervous system, and in its capacity as a base helps to regulate the p_H concentration of the blood. The appearance in the circulation of toxic nitrogenous by-products will therefore deplete this reserve, causing a negative calcium balance, a hypersensitivity of the peripheral neurones, and an upset in the normal $\frac{[H^+]}{[OH^-]}$ mechanism. The administration of calcium salts, the withdrawal of blood or the dilution of the circulating poisons by saline all naturally alleviate the symptoms of tetany, and tend to break the vicious circle that has been formed.

SUMMARY

Tetany is a metabolic disorder, characterized clinically by peripheral nervous hyperexcitability and by intermittent spasms of the limbs.

It may arise either as a disease sui generis (idiopathic tetany) or as a complicating factor in the course of other morbid or physiologic states.

Tetany is essentially an intoxication by nitrogenous by-products which may appear under a great variety of conditions.

There is no evidence that parathyroid upset is the cause of the symptoms in any variety except tetania strumipriva.

The acid base mechanism and the calcium metabolism may be secondarily affected in tetany.

BLOCK OF THE BRANCHES OF THE BUNDLE OF HIS *
CLINICAL NOTES ON THE CHANGES FOLLOWING THE ADMINISTRATION
OF DIGITALIS, COMMENTS ON THE LEVOCARDIOGRAM,
DEXTROCARDIOGRAM AND BICARDIOGRAM

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A lesion of a branch of the bundle of His is not as rare as is commonly supposed. It is one of the heart defects that can only be detected by means of electrocardiographic records, and because these are often difficult to secure a great many of these cases are unrecognized. One who has the opportunity of studying large numbers of heart defects with the aid of electrocardiograms is able to make this diagnosis at fairly frequent intervals.

The facts presented in this paper are based on a study of twenty-five cases seen in the last six years. For this purpose only those cases which show curves that are generally accepted as typical of this lesion have been selected, the cases showing graphic records of a less characteristic type will not be considered at the present time.

The following criteria have been used in selecting curves which are included in the present group:

- 1 Q-R-S interval exceeds 0.1 second
- 2 Q-R-S showing a considerable amplitude
- 3 Q-R-S notched in the leads of considerable amplitude
- 4 T' large and opposite in direction to the main deflection of Q-R-S

As to the type of curve characteristic of a lesion of the right as contrasted with a lesion of the left branch of the bundle, there is still a difference of opinion.¹ The records secured from experimental animals are not constant and must be used with much caution in interpreting the lesions in man. Further, the pathologic evidence is quite conflicting. We have no new evidence to offer in the solution of this

* Read by title before the American Society for Clinical Investigation, Atlantic City, May 5, 1924.

1 Eppinger and Rothberger Ueber die Folgen Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr f klin Med **70** 1, 1910
Eppinger and Stoerk Zur Klinik des Elektrokardiograms, Ztschr f klin Med **71** 157, 1910
Cohn and Lewis The Pathology of Bundle Branch Lesions of the Heart, Proc New York Path Soc **14** 207, 1914
Lewis The Spread of the Excitatory Process in the Vertebrate Heart, Phil Tr Roy Soc London **207** 221, 1916
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Oppenheimer and Pardee The Site of the Cardiac Lesion in Two Instances of Intraventricular Heart Block, Proc Soc Exper Med & Biol **17** 177, 1920

phase of the subject and therefore will not discuss it. For the purposes of the present paper we will use the most widely accepted interpretation, namely (1) The main deflection of the Q-R-S group directed upward in Lead I and downward in Lead III indicating a lesion of the right branch, (2) the main deflection of the Q-R-S group directed downward in Lead I and upward in Lead III indicating a lesion of the left branch.

As a rule the history, physical signs and course of these cases have no clue in them to distinguish them from cases of chronic myocarditis with gradually advancing cardiac insufficiency. Certain patients who presented evidence of a complete auriculoventricular block, in conjunction with a defect of a branch of the bundle, have shown the bradycardia and sometimes the attacks of unconsciousness characteristic of the Adams-Stokes syndrome.

The treatment of these cases of bundle branch block has been most unsatisfactory. In a number, the administration of atropin, epinephrin and thyroxin has been carefully studied but the changes produced have been of little moment and have always been transitory. In only five of the twenty-five cases was there definite evidence of a syphilitic infection, to these, antisyphilitic treatment was administered with little if any noticeable effect on the heart. Rest, measures directed to the correction of the abnormal renal function and in some cases digitalis have seemed to be our only dependable allies.

Of the twenty-five patients, sixteen were men and nine women. Twenty were over 50 years of age when the graphic record of a bundle branch lesion was secured. Three patients were between 30 and 40 years of age, two between 40 and 50, fourteen between 50 and 60 and six between 60 and 70.

Four of these patients have disappeared from sight and the outcome is unknown. Of the remaining twenty-one, only three are living, one of these has been under observation for four years, the others for fourteen and ten months respectively. Eighteen are dead, most of them died within six months after the electrocardiographic record showing the bundle branch lesion was obtained, two of them lived for over one year, one for three and a half years.

Chart 1 shows the electrocardiographic records of three leads secured from a woman, aged 60 years, who lived for three and one half years after the diagnosis of this defect was made. The curves present all the characteristics of a lesion of the right branch of the bundle, the Q-R-S complex is of considerable amplitude, is notched and requires 0.14 second for its completion, the T' wave is large and opposite in direction to the main deflection of Q-R-S. The principal ventricular deflection is directed upward in Lead I and downward in Lead III. This presents the type of curve most frequently encountered.

In Charts 2 and 3 curves are presented, interpreted as indicating lesions of the left branch of the bundle. A lesion of the left branch of the bundle is an exceedingly rare finding, in our series of twenty-five cases these are the only ones we have seen. A review of the literature indicates that others have observed them very rarely. The reason for the greater frequency of damage to the right bundle is not altogether clear. It has been explained by the anatomic differences in the two branches. The left branch subdivides soon after its origin from the

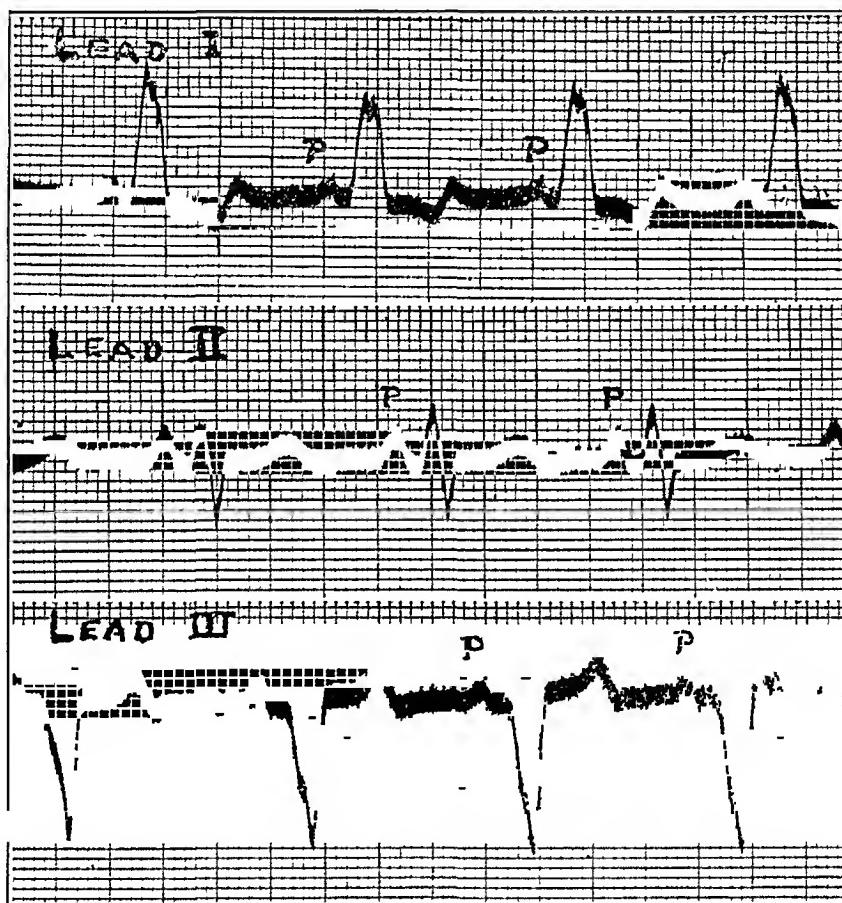


Fig 1.—Right bundle branch block. Levocardiogram, written primarily by the left ventricle

main stem, spreading out over the interventricular septum, while the right branch is continued as a single strand for a considerable distance. It would therefore be more easily destroyed by a single small lesion.

The records shown in Chart 2 are from a patient seen in consultation in February, 1923. He was a man, aged 47, who had been perfectly well until November, 1922. At that time he had an attack of unconsciousness and the heart was found to be irregular with a rate of 60. In December he had a second attack in which he was unconscious but the heart rate was not observed. The third attack occurred in

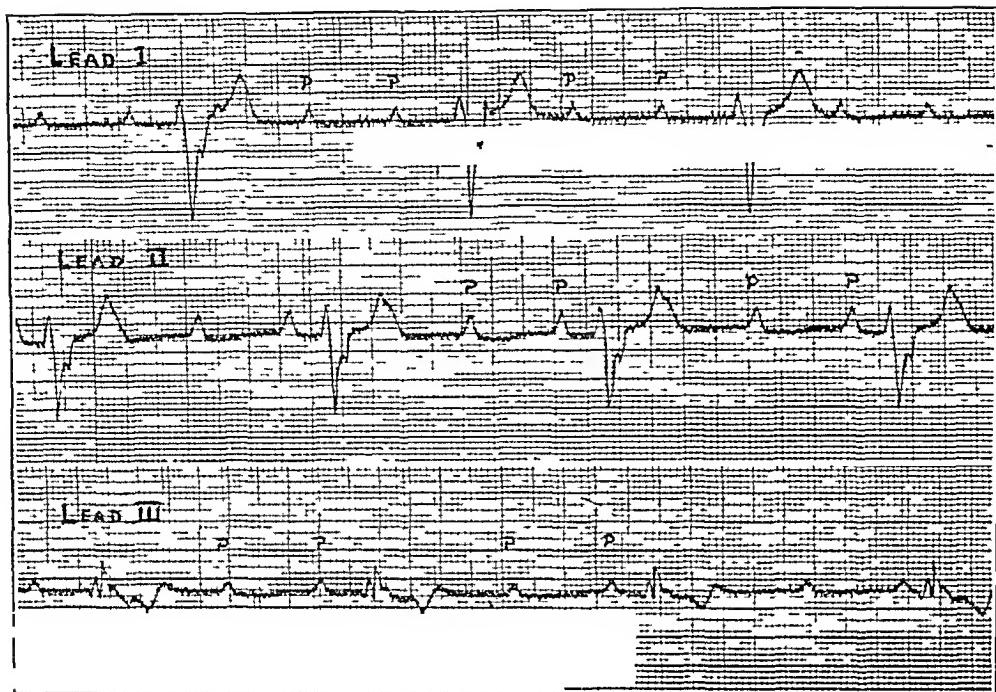


Fig 2—Dextrocardiogram, written primarily by right ventricle Associated block of the bundle of His

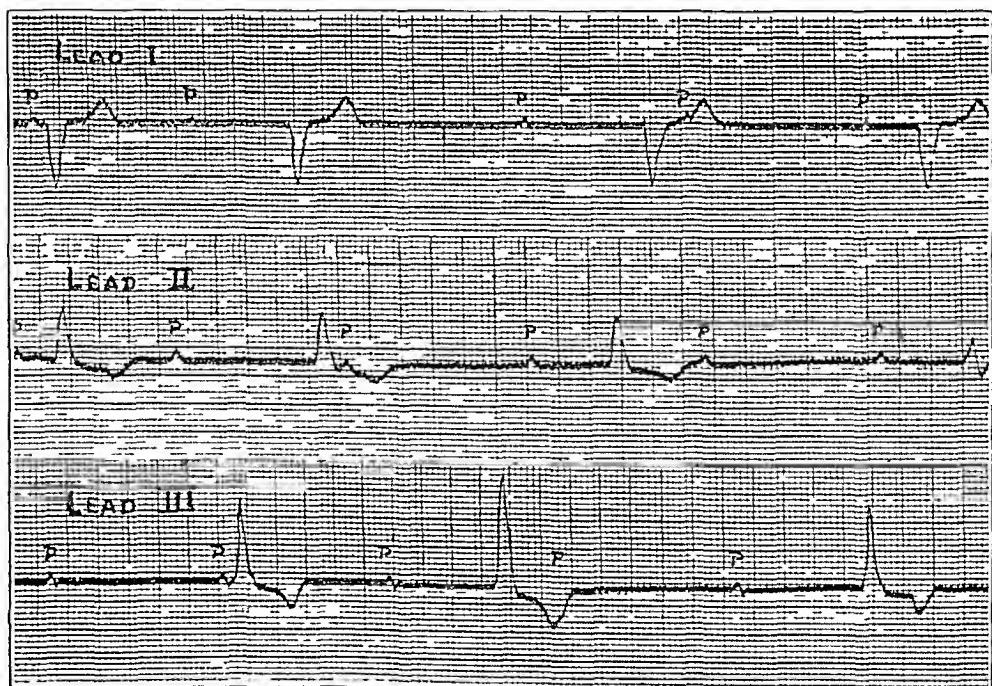


Fig 3—Dextrocardiogram, written primarily by right ventricle Associated block of the bundle of His

January, 1923, when he fell in the bathroom and was unconscious for some minutes, the heart rate was 28 and since that time has never exceeded 39 per minute. It has never been possible to discover a satisfactory explanation of the cause of the heart lesion. The heart was not enlarged and no murmurs could be detected. The effect of atropin, epinephrin and thyroxin were studied without any appreciable influence on the block. He is still living but has attacks of unconsciousness at irregular intervals.

The other patient giving a curve (Chart 3) of a lesion of the left branch of the bundle was a single man, aged 48, a traveling salesman, seen in consultation in May, 1923. He is still living. As a child he had diphtheria, and gonorrhea as a young man. There were no other illnesses. He denied any syphilitic infection, and the blood Wassermann had been negative on several occasions. For a year he had felt weak and had many attacks of dizziness but had never actually lost consciousness. At times his heart "thumped" and he was a little short of breath. His heart was considerably enlarged, rate 28, sounds of good quality, no murmurs. Blood pressure, systolic 125, diastolic 50. Slight edema of the ankles. Before I saw him he had been given several courses of mercury, potassium iodid and arsphenamin without any appreciable effect. Later atropin, thyroxin and epinephrin were each tried but failed to influence the condition of block.

It is interesting to note that in both of these cases classified as lesions of the left bundle, there is associated a complete or partial block of the A-V bundle. This suggests the thought that the lesion producing the defect has invaded a portion of the main stem and the entire left bundle before it has reached the point where it subdivides.

The digitalization of these cases of bundle branch block affords several points of interest:

- 1 The patients usually develop extrasystoles at a comparatively early stage of digitalization.
- 2 The extrasystole is usually (not invariably) initiated in the ventricle opposite to the one in which the bundle is intact.
- 3 The Q-R-S complex is prolonged.
- 4 The T' deflection is prolonged and increased in amplitude.

All of these features are illustrated in Chart 4. These records were secured from a man, aged 57, suffering from marked symptoms of cardiac insufficiency and attacks of precordial pain. He had a history of rheumatism when he was 27 and syphilis at 32. The blood Wassermann was positive. He presented a greatly enlarged heart with mitral and aortic valve lesions and a dilated aorta. Four months later he died very suddenly from a thrombosis of the right coronary artery. The curves indicate the changes in the three leads produced by digitalization.

Chart 5 is from a woman, aged 67, who is still living and has been under observation for four years. She has a general arteriosclerosis, an enlarged heart with lesions of the mitral and aortic valves and a dilated aortic arch. The etiology is obscure. There is no history of syphilis and the blood Wassermann reaction has been found negative repeatedly. She has had an auricular fibrillation and attacks of cardiac insufficiency during the whole period of observation. The records are presented for the purpose of comparing the curves obtained before and after the administration of digitalis. The electrocardiograms of each of these cases show a lesion of the right branch of the bundle. As has been pointed out by Lewis and by Wilson, the initial portions of the usual ventricular complex in these cases is written by the left ventricle (the "levocardiogram"). After digitalis was administered, extrasystoles appeared which arose in the right ventricle and the "dextrocardiogram" was written. It seems quite possible that these extrasystolic contractions may arise in the right branch of the bundle distal to the pathologic lesion.

The prolongation of both the Q-R-S group and the T' complex indicates that digitalis has a very definite influence in inhibiting the rate of conduction in the ventricular tissues and is a corroboration of the observations on changes in the T-wave made by Cohn, Fraser and Jamieson in 1915.² These alterations also emphasize the generally recognized fact that digitalis has a much greater influence in hearts presenting pathologic changes than in those with normal tissues.

Lewis³ in his studies of the spread of the excitatory process in the heart both experimentally in animals and in human records has charted the curves which are produced when the stimulus is received by one ventricle and then passes through the septum to activate the other ventricle. When the left ventricle primarily receives the stimulus the "levocardiogram" is written, when the right ventricle is the first to be stimulated the "dextrocardiogram" is recorded. The curve written by the ventricles of the normal subject (the "bicardiogram") is the algebraic sum of the "levocardiogram" and the "dextrocardiogram." Wilson⁴ has studied the same subject by a clever and most original method, he cut the right branch of the bundle and recorded the "levocardiogram," he then stimulated the right ventricle and obtained the curve of the extrasystolic "dextrocardiogram." By introducing the

2 Cohn, Fraser and Jamieson. The Influence of Digitalis on the T-Wave of the Human Electrocardiogram, *J Exper Med* **21** 593, 1915.

3 Lewis. The Spread of the Excitatory Process in the Vertebrate Heart, *Phil Tr Roy Soc London* **207** 221, 1916.

4 Wilson, F N, and Herrmann, G R. Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, *Heart* **8** 229 (May) 1921.

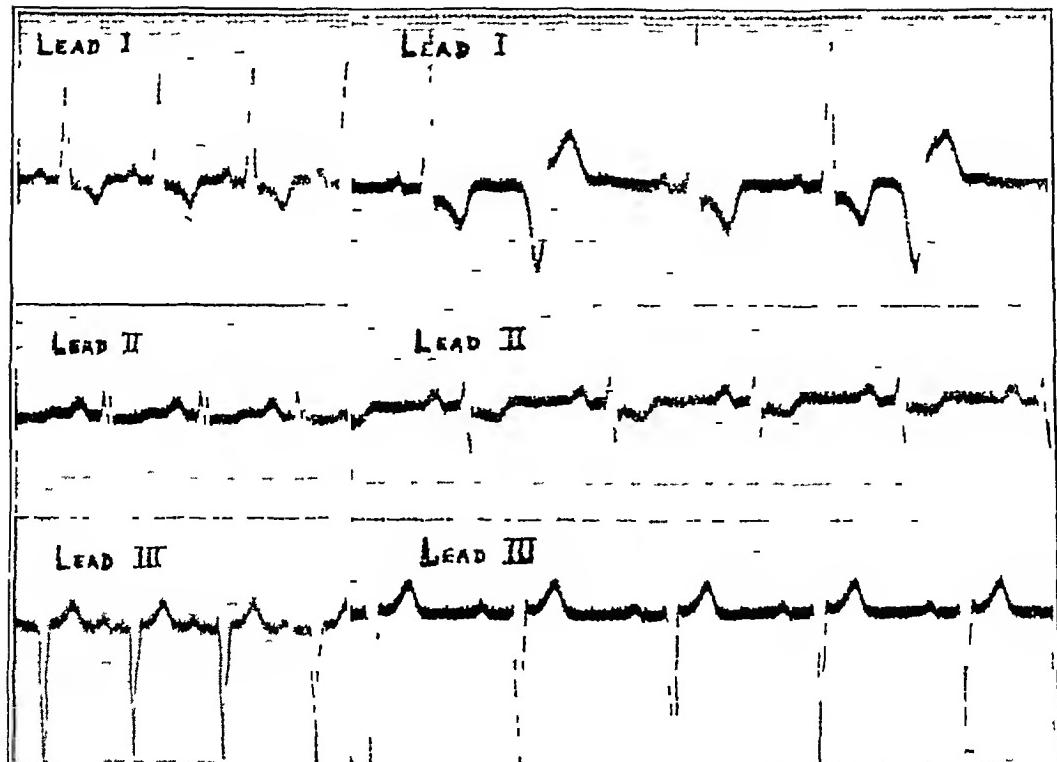


Fig 4.—Before digitalis (left). After digitalis (right). Right bundle branch block Levocardiogram. After digitalis two extrasystolic dextrocardiograms, Q-R-S prolonged, T' prolonged and amplitude increased

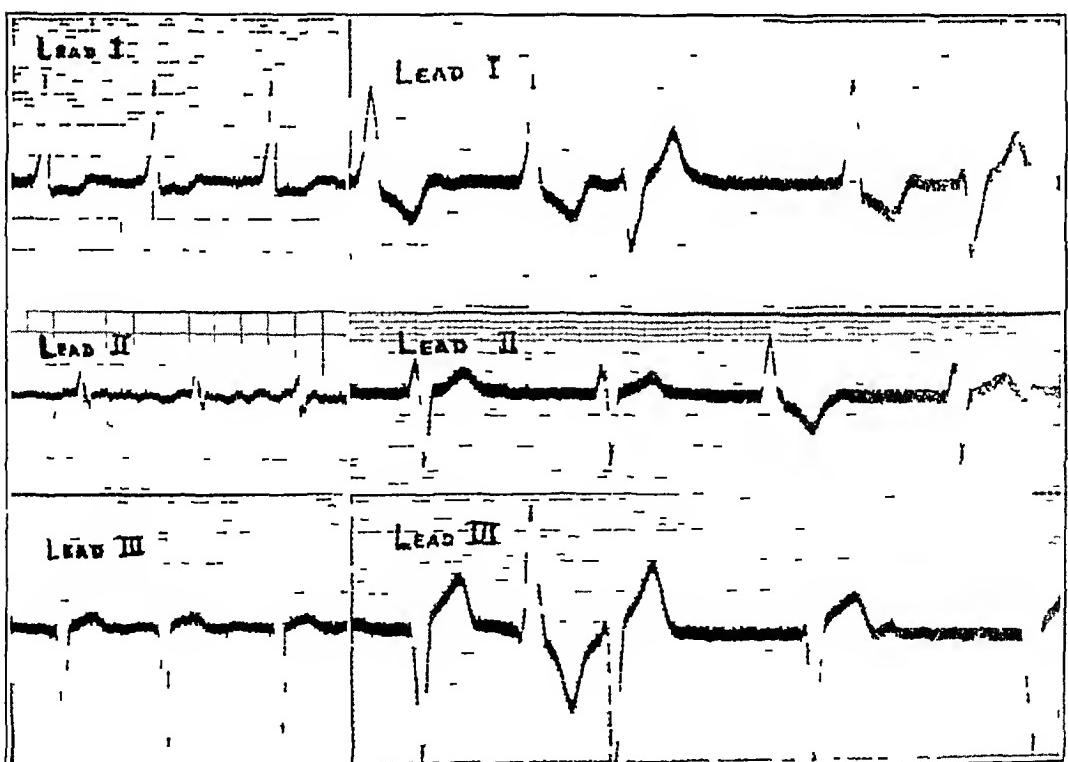


Fig 5.—Before digitalis (left). After digitalis (right). Auricular fibrillation Right bundle branch block Levocardiogram. After digitalis many extrasystolic dextrocardiograms Q-R-S prolonged, T' prolonged, amplitude increased

stimulus at the proper time so that the normal stimulus and the artificial stimulus were coincident, both ventricles were simultaneously activated and the curve written was the normal "bicardiogram."

In the clinic we occasionally encountered curves which have so many points of similarity to the curves which Wilson obtained experimentally that we are impelled to interpret them as produced by a corresponding mechanism.

In Charts 4 and 5 the stimuli coming down through the bundle activate the left ventricle and the "levocardiogram" is written, under the influence of digitalis the right ventricle becomes irritable and

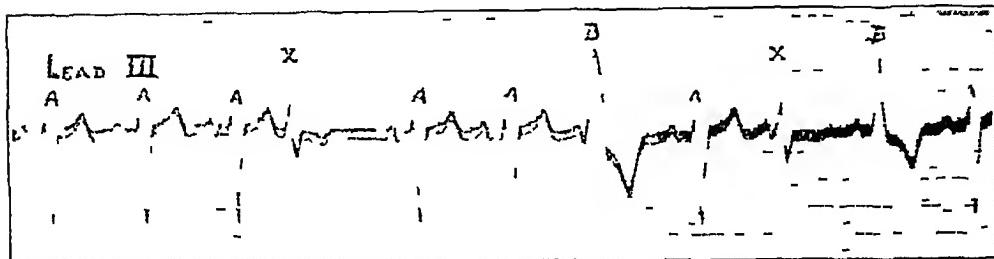


Fig 6—Lead III only Right bundle branch block Complexes A, levocardiograms Complexes B, dextrocardiograms Complexes X, bicardiograms

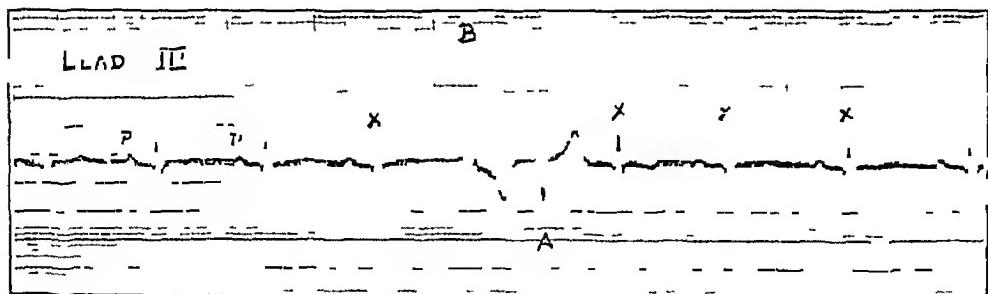


Fig 7—Lead III only X, normal ventricular bicardiograms A, extrasystolic levocardiograms B, extrasystolic dextrocardiogram

occasionally an extrasystolic "dextrocardiogram" appears. If, as Wilson has done experimentally, we could superimpose one of these curves on the other in the proper time relation the "bicardiogram" normal for this person would be recorded.

In Chart 6 is presented a curve which we believe may be explained by the mechanism that has been suggested. The record was obtained from a man, aged 55, a machinist, who was suffering from a general arteriosclerosis with cardiac hypertrophy, with a history of numerous attacks of cardiac insufficiency covering a period of five years. There was no definite history of infections of any kind, no rheumatism, the

blood Wassermann test was negative He had edema of the legs and hydrothorax He died suddenly a few days after the record here presented was taken

Only Lead III is reproduced We interpret this curve as indicating a lesion of the right branch of the bundle The complexes marked "A" are characteristic levocardiograms written by the left ventricle in response to normal supraventricular stimuli The complexes marked "B" are extrasystoles originating in the right ventricle (dextrocardiograms) We suggest that the complexes marked "X" are bicardiograms due to the simultaneous activation of the right and left ventricles

A similar explanation is offered in the interpretation of Chart 7 This is the record from a man, aged 30, who supposed he was in perfect health with no subjective symptoms of any description The irregularity of the heart was discovered in the course of a routine examination for life insurance and he was referred to me for further study and for an opinion as to his insurability Only Lead III is reproduced This curve is not one of bundle branch block, but is included in this series because it illustrates so well the extrasystolic levocardiogram, the extrasystolic dextrocardiogram and his normal bicardiogram In this case the ventricular irritability was caused by the very excessive use of tobacco

SUMMARY

Lesions of the right branch of the bundle of His are not uncommon

Lesions of the left branch are rare, the electrocardiographic curves of two cases associated with complete A-V block are presented and discussed

These lesions have been seen only in cases of advanced heart disease and a high mortality is to be expected

The administration of digitalis produces conspicuous changes in the graphic records

Several curves are presented illustrating the clinical analogues of the dextrocardiogram, levocardiogram and bicardiogram which others have produced experimentally

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OBSERVATIONS ON A CENTRIPETAL VENOUS PULSE IN MAN¹

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If one seals a glass capsule over a superficial vein on the back of the hand and applies to this capsule an air pressure a few millimeters of water lower than the minimum pressure required to produce complete collapse of the vein, a distinct pulsation of the vein with each heart beat will be seen in a certain number of subjects. That this pulse is not transmitted directly back from the heart, as is the jugular pulse, is shown by the fact that the pulse persists after compression of the vein just central to the capsule. The pulsations are abolished by compression of the vein just peripheral to the capsule. It would appear that we are dealing with a pulse passing from the arteries through the capillaries and venules into the larger veins. With this idea in mind, certain procedures calculated to modify the extent to which a pulse could be propagated from the arterial to the venous side of the circulatory bed were carried out. These procedures were exercise and the application of heat and of cold.

The subject sits in the apparatus designed for stationary exercise described in a recent paper¹. The pressure in the capsule is applied by the admission of compressed air². Exercise consists in the lifting of 5 kg weights by extension of the legs, the exercise period being five minutes. Heat was applied by partially immersing the hand in water at 45 C, cold by partial immersion in water at 5 C. Some subjects under no circumstances showed a venous pulsation. Others showed no pulse under control circumstances but it appeared on application of heat. A third group showed a pulse under control circumstances, this persisted and seemed to be somewhat accentuated on application of heat. In all cases the pulse was abolished on application of cold. A five minute exercise period seemed to have no influence in determining the presence or absence of the pulse. In one subject, who showed no pulse at rest, a fifteen minute period of exercise to the point of sweating brought out the pulse. In all cases where the venous pulsation is seen, the pulse at the radial artery is felt a fraction of a second before the venous pulse.

* From the Physiological Department of Washington University

1 White, H L Circulatory Responses to Exercise in Man and Their Bearing on the Question of Diastolic Heart Tone, Am J Physiol 69 410 (July) 1924

2 White, H L Observations on Venous Pressure and Skin Blanching Pressure by a Modified Method, Am J Physiol 69 10 (June) 1924

is seen. No attempt has been made to measure this interval quantitatively. A table illustrating some of the positive results is given, the presence or absence of the venous pulse being indicated.

Positive Results, Showing Presence or Absence of Venous Pulse

				Subject Z Age 55
Control	Heat	Cold	Exercise	
absent	present	absent	absent	no compression
absent	present	absent	absent	central compression
absent	absent	absent	absent	peripheral compression
				Subject H Age 21
Control	Heat	Cold	Exercise	
present	present	absent	absent	no compression
present	present	absent	absent	central compression
absent	absent	absent	absent	peripheral compression
				Subject D Age 28
Control	Heat	Cold	Heavy Exercise	
absent	present	absent	present	no compression
absent	present	absent	present	central compression
absent	absent	absent	absent	peripheral compression

Our interpretation of these results is that in certain subjects heat and heavy exercise dilate the arterioles and capillaries to the extent that the pulse from the arteries is permitted to pass to the venous side. On heavy exercise, the increased pulse pressure also must play a part. With some subjects this condition obtains at rest, while with others it cannot be brought about even by the application of heat or by exercise. The constriction of the arterioles and capillaries by cold damps out the pulse. By the time the pulse reaches the venous side it possesses only a small amount of energy. It is thus not surprising that a manometer connected with a cannula in a vein should fail to register a pulse. The pulsations become evident only when the conditions are such that the maximum oscillations of the vessel wall are produced, i.e., when the externally applied pressure equals the diastolic venous pressure. Attempts to measure the pulse pressure in the vein on the basis of this principle have not proved practicable since the difference between systolic venous pressure (the minimum pressure required to produce complete collapse of the vein) and diastolic venous pressure (the pressure at which the maximum pulsations are seen) is at the most only a few millimeters of water.

Lewis³ has recently reported localized "capillary pulsation" on the local application of heat. He finds on microscopic examination that

³ Lewis, T. Observations upon Capillary Pulsation, *J. Physiol.* 58: 21, 1924.

the venules as well as the capillaries participate in this pulsation. He has traced the pulsation as far as "the larger venules of the sub-papillary plexus" but makes no mention of having observed a pulse in large superficial veins. He finds that the pulse in the venules is centripetal, which agrees with our present findings on large veins. Krogh and Rehberg,⁴ working with microscopic preparations of the bladder of the frog, find that the pulse wave penetrates capillaries but is annihilated by interference in the venules. It is apparent that this is not necessarily the case in man. Lewis also finds that "in middle life and more advanced years the reaction to heat, described in the foregoing, is usually reduced or absent, suggesting that the arterioles have lost, partially or completely, their power to expand." We have not found any definite relation between age and the venous pulse. A number of young subjects, aged from 20 to 25 years, have failed to show the pulse on exercise or application of heat, while of two middle-aged subjects available, one, aged 42, failed to show a pulse, the other, aged 55, showed no pulse under control circumstances, but it appeared on application of heat.

In view of the fact that it does not appear to be generally recognized, judging from the statements in current physiology texts, that a centripetal venous pulse propagated through the capillaries from the arteries may exist in normal subjects, it is interesting to note that King⁵ in 1837 observed, with the aid of a mirror, pulsations of the large median veins of his own forehead while lying on his back about a half hour after dinner. He attributes this to the passage of the arterial pulse through the capillaries into the vein, but apparently did not exclude the possibility of a centrifugal pulse from the right heart. The same can be said of some of his observations on pulsations of veins on the back of the hand. The presence of valves need not necessarily block a retrograde pulse. More convincing, however, is King's reference to "an old experiment, to immerse the hand in warm water previous to and during venesection, when the jet of blood is distinctly seen to increase with each arterial pulse." He adds that this experiment will not always succeed. I believe that King is justified in his remark that this behavior of the escape of venous blood "is a sufficient proof that the impulse of the left ventricle is not always completely expended on the arterial or even on the capillary system."

Benson⁶ refers to the escape of venous blood *per saltum* in one of his patients. This patient also showed distinct pulsation of the veins.

4 Krogh, A., and Rehberg, P. B. Kinematographic Methods in the Study of Capillary Circulation, Am J Physiol 68:153 (April) 1924.

5 King, W. T. An Essay on the Safety-Valve Function in the Right Ventricle of the Human Heart, Guy's Hosp Rep 2:104 (series 1) 1837.

6 Benson, C. Case of Pulsation in the Veins of the Upper Extremities, Dublin J M Sc 8:324 (series 1) 1836.

of the upper extremities Benson concludes that this pulsation depends on regurgitation from the right heart rather than a pulse from the left heart passing through the capillaries Stokes⁷ refers to this case, and agrees with Benson as to the mode of production of the pulse It is difficult for me to see how such a view can be held A necropsy showed that the venous valves were completely competent, and while I will readily admit that a retrograde pulse wave may well pass competent valves I cannot see how blood could be regurgitated A more reasonable explanation is a centripetal pulse coming via the arteries and capillaries Quincke⁸ reports a centripetal pulse in the veins of the back of the hand in his own case and in two other cases without aortic insufficiency, one of these patients, however, presumably had paralysis of the vaso-motor nerves to the region where the pulse was seen He also reports four cases of aortic insufficiency, with presumably a high pulse pressure, in which the venous pulse was evident He does not appear to recognize that the pulse may be of frequent occurrence in normal persons "Under proper conditions, which may, in part, occur only pathologically, but which lie, in part, also within the limits of the normal, the pulse wave passes to the capillaries and even on into the veins" (Unter passenden Bedingungen, wie sie zum Theil nur pathologisch vorkommen, zum Theil aber auch durchaus in den Grenzen der Norm liegen, pflanzt sich die Welle bis in die Capillaren und selbst bis in die Venen fort) In a later paper⁹ Quincke further states that certain conditions are necessary for the production of the centripetal venous pulse, a considerable relaxation of the arterioles, a powerful heart beat, preferably with a high pulse pressure and, for its visualization, a thin skin and a certain medium degree of venous filling The pulse is thus seen most frequently in fevers and is seen in normal subjects only when a high temperature has produced a marked vasodilatation As was first suggested by Quincke, and later by Jürgensen,¹⁰ the direct anastomoses between arterioles and venules reported by various anatomists may play a part in the production of the centripetal venous pulse

It is apparent that Quincke's failure to recognize that this pulse is of rather frequent occurrence in normal subjects, even at ordinary temperatures, is due to the fact that he merely observed the veins without subjecting them to any external pressure Under these condi-

7 Stokes, W Diseases of the Heart and Aorta, 1855, p 219

8 Quincke, H Beobachtungen über Capillar-und Venenpuls, Berl klin Wchnschr **5** 357, 1868

9 Quincke, H Ueber Capillarpuls und centripetalen Venenpuls, Berl klin Wchnschr **27** 265, 1890

10 Jürgensen, E Microkapillarbeobachtungen, Deutsches Arch f klin Med **132** 204 (May) 1920

tions only relatively powerful pulsations could be recognized. Our success in demonstrating the pulse in a rather high percentage of normal subjects has been due to our subjecting the vein to a pressure at which the maximum oscillations of the vessel wall are brought out.

SUMMARY

Evidence is presented that a pulse may pass from the arterial to the venous side of the circulatory bed in normal subjects, and can be demonstrated in the large superficial veins.

THE VOLUME AND COMPOSITION OF THE BLOOD AND THE CHANGES INCIDENT TO DIU- RESIS, IN CASES OF EDEMA

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The idea is prevalent among physicians that hydremia or hydremic plethora is the rule in cases of edema. This impression is based on (1) the pallor or so-called pasty appearance of the skin, (2) the decrease in urinary output, (3) the accumulation of water in the subcutaneous tissues or in the serous cavities, and (4) the decrease, in certain cases, in the percentage of solids, hemoglobin, albumin, erythrocytes, and so forth, in the blood and plasma. Although these findings are suggestive of an edematous or watery state of the blood, that is, of dilution of the blood by water which has failed of excretion, there has long been a wish that this general impression might be supported by more tangible and conclusive evidence.

Edema, although a familiar clinical phenomenon and the subject of innumerable investigations, is at present far from being understood. Since its experimental production is difficult, indeed practically impossible, our knowledge of the condition of the blood in cases of edema has been, and for the present must continue to be, derived from clinical sources. We know, however, that physicochemical processes, involved in the interchange of water between the blood and tissues, play a striking part. In the study of this interchange of fluid, the great importance of data pertaining to the volume and composition of the blood is obvious. In fact, such data are essential in determining whether changes occurring in liquid and solid constituents of the blood are actual or relative. Lack of suitable methods of determining blood and plasma volumes during life have been responsible for the dearth of data relative to absolute values. With the advent of the dye method of determining circulating blood and plasma volumes, this difficulty has been diminished to a great extent, and it seems highly desirable at this time to investigate again the subject of the concentration and volume of the blood in relation to edema.

Various Conceptions of Hydremia.—In reviewing the literature on the composition of the blood in cases of edema, the terms "hydremia," "hydremic plethora" and "hydremic state" constantly occur. Bright observed the watery condition of the blood in the edema of nephritis and attributed this to loss of albuminous substances into the urine with

thinning of the blood Stewart introduced the term hydremic plethora to indicate a dilution of the blood by the addition of water Cohnheim,¹ in his classical studies on hydremia and anhydremia in relation to edema, says "The blood is hydremic when the contained water is absolutely or relatively increased" In case of absolute increase, the total amount of solid constituents in the blood (chiefly albumin) remains unaltered, but the amount of water is increased In case of a relative increase, the albumin is diminished, while the weight and volume of the water are normal Cohnheim also recognized a third theoretic possibility, that of diminished albumin content associated with an increased total content When this combination of changes occurs, it must indeed cause an especially severe degree of hydremia Dieballa² narrowed the conception of hydremia to a condition in which the plasma solids are relatively or absolutely decreased A relative decrease is caused by an increase of the total blood with dilution of the solids, that is, by hydremic plethora, while an absolute decrease is due to an actual loss of plasma proteins

Boycott³ found that in the edema of experimental uranium nephritis in animals, the blood, as well as the tissues, was affected, and that the condition was associated with serous effusions Hemoglobin values were employed as criteria of the so-called hydremia Volhard⁴ asserts that blood dilution or hydremia, with a relative decrease of erythrocytes of from 1,000,000 to 2,000,000, is often associated with glomerular nephritis, but that this condition does not predominate in cases in which the edema is marked He cites Ebert, who, using Bang's micromethod for estimating blood water, finds that blood water and edema are inversely related in certain cases The blood water may be lowest in the periods of greatest edema, it may increase with absorption, and may even further increase with the restoration of the glomerular function A lowering of the erythrocytes for each unit volume and an increase in blood volume have been observed in this later period Volhard calls attention to the loose usage of the term hydremia He would limit it to indicate a condition of the blood in which there is an actual dilution, with a resulting percentage reduction of the cellular elements He questions its usage in relation to conditions in which the blood merely exhibits diminished solids

1 Cohnheim, J. Lectures on General Pathology, a Handbook for Practitioners and Students, London, New Sydenham Society, 1889, p 447

2 Dieballa, G., and Ketly, V. Ueber die Wechselbeziehung von Albuminurie, Hydramie, und Hydrops bei Brightikern, Deutsch Arch f klin Med **61** 76-90, 1898

3 Boycott, A. E. The Regulation of the Blood Volume in Normal and Nephritic Animals, J Path & Bacteriol **18** 498-512, 1913-1914

4 Volhard and Fahr. Die doppelseitigen hematogenen Nierenerkrankungen, Berlin, Julius Springer, 1918

Keith, Rowntree and Geraghty,⁵ in their original report on the use of the vital red method of determining blood volume, noted no significant changes in plasma volume during the period of diuresis in a case of renal edema. Bock,⁶ using the dye method for estimating plasma volume in case of edema, found no disturbance of the relationship between plasma volume and body weight. Lindner, Lundsgaard and Van Slyke⁷ studied the plasma proteins in cases of nephritic edema, and found that actual depletion, and not dilution, was the basis for the low protein values. The amount of the total plasma protein for each kilogram of body weight was definitely diminished (from 15 to 30 gm), the normal values being from 30 to 50 gm. The body weight was corrected for the probable additional weight of edema fluid.

There is considerable difference of opinion with regard to the state of the blood in cases of cardiac edema. Many investigators maintain that a normal water content of serum is present, Strauss⁸ and Veil⁹ believe that increased water content of serum exists in certain cases. Chiray¹⁰ has observed increased concentration of the blood in certain stages of cardiac edema. Bolton,¹¹ in an experimental study of cardiac edema produced by partial obstruction of the inferior vena cava, using the Welcker method for determining blood volume, found hydremic plethora, which subsequently became converted into a true plethora by the entrance of erythrocytes into the blood. There are no available data on the volume and composition of the blood in cases of diabetic edema.

To correlate the diverse conceptions, held at the present time, of the composition of the blood in cases of edema is almost impossible, because of (1) lack of data relative to absolute values in relation to the solids and water of the blood and plasma, (2) lack of comparative data in the different types of edema, and (3) confusion and inadequacy of terms used in relation to blood states. In the work herein reported,

5 Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16** 547-576 (Oct.) 1915.

6 Bock, A. V. The Constancy of the Volume of the Blood Plasma, *Arch. Int. Med.* **27** 83-101 (Jan.) 1921.

7 Lindner, J. C., Lundsgaard, C., Van Slyke, D. D., and Stillman, E. The Cause of Low Plasma Protein Concentration in Nephritis, *Proc. Soc. Exper. Biol. & Med.* **20** 319, 1923.

8 Strauss, H. Untersuchungen über den Wassergehalt des Blutserums bei Herz- und Nierenkranken, *Ztschr. f. klin. Med.* **60** 501-505, 1906.

9 Veil, W. H. Ueber die klinische Bedeutung der Blutkonzentrationsbestimmung, *Deutsch. Arch. f. klin. Med.* **112** 504-538, 1913, *ibid.*, Ueber die klinische Bedeutung der Blutkonzentrationsbestimmung, *Deutsch. Arch. f. klin. Med.* **113** 226-260, 1914.

10 Chiray, M. Dilution et concentration du sang, *Presse med.* **16** 19-22, 1908.

11 Bolton, C. Further Observations on the Pathology of Cardiac Dropsy, *J. Path. & Bacteriol.* **20** 290-326 (Jan.) 1916.

we have attempted to obviate some of these difficulties by collecting data in different types of edema, by the correlation of absolute and relative volumes, and by use of new terms to indicate the volume states

New Terminology for Volume States of the Blood—In view of the conflicting interpretations of hydremia, hydremic states, hydremic plethora and polyemia, and of the resultant confusion, it seems wiser to avoid the use of these terms in discussing blood volume. If the term hydremia is to be retained, we believe it should be limited to indicate increased water content of plasma. With these points in mind, terms as follows are suggested: (1) normovolemia for normal blood volume, (2) hypervolemia for increased blood volume, and (3) hypovolemia for

TABLE 1—Classification and Suggested Terminology of Volume States of the Blood

Normovolemia for Normal Blood Volume

- A Simple normovolemia for normal ratio of cell to plasma volume
- B Polycythemic normovolemia for increased ratio of cell to plasma volume
Synonym—Concentrated blood
- C Oligocytathemic normovolemia for decreased ratio of cell to plasma volume
Synonym—Anemia

Hypervolemia for Increased Blood Volume

- A Simple hypervolemia for normal ratio of cell to plasma volume
Synonym—Simple plethora, observed in certain types of edema
- B Polycythemic hypervolemia for increased ratio of cell to plasma volume
Synonym—Polyemia vera
- C Oligocytathemic hypervolemia for decreased ratio of cell to plasma volume
Synonym—Hydremic plethora, seen in some anemias

Hypovolemia for Decreased Blood Volume

- A Simple hypovolemia for normal ratio of cell to plasma volume
Synonym—Simple oligemia, observed immediately following blood loss and in certain cases of edema and obesity
- B Polycythemic hypovolemia for increased ratio of cell to plasma volume
Synonym—Anhydremic oligemia. Anhydremia, observed in shock and dehydration states
- C Oligocytathemic hypovolemia for decreased ratio of cell to plasma volume
Synonym—Oligocytathemia, occasionally observed in anemias

decreased blood volumes. These terms are self-explanatory and apply only to volume states. Obviously, the cell plasma volume ratio also is important, entering into consideration in all physiologic or pathologic changes in volume and composition of the blood. In expressing this ratio, modifying terms may be employed, such as (1) simple for normal cell plasma volume ratio, (2) polycythemic for increased cell plasma volume ratio, and (3) oligocytathemic for decreased cell plasma volume ratio (Table 1).

Types of Cases Studied¹²—The present study embraces (1) three cases of cardiac edema,¹³ (2) three of diabetic edema, (3) four of subacute glomerular nephritis with edema, and (4) four of subacute nephrosis.

12 These cases were uncomplicated by an acute or subacute infection such as rheumatism, endocarditis or nephritis.

13 The clinical diagnoses were made independently by clinicians to whom the cases were assigned.

Method of Collecting Blood—Blood was taken from the patient between the hours of 8 and 9 a m, with the patient at rest and fasting, and no fluids having been taken. The blood and plasma volumes in relation to body weight were calculated for the postedema period. As the period between the edema and postedema estimations was relatively short, in all but one case, the error incident to weight changes, other than those caused by water loss, was small, and would not, of course, invalidate the total volume values.

Treatment—The standard Kaseil diet with digitalization was routinely employed in the cases of cardiac edema. The fluid intake was restricted for the entire period between the estimations. Massive calcium treatment with moderately restricted fluids was given in cases of the diabetic type of edema, besides the specific treatment for diabetes.

The usual salt free, low protein regimen was the rule in cases of glomerular nephritis. In Cases 7 and 10, abdominal paracentesis was performed, in Cases 8, 9 and 10, sweating and calcium treatment were employed without results; in cases of nephrosis, the treatment consisted of salt free diet and fluids restricted to from 600 to 800 c.c. Massive doses of calcium were tried in Case 11 without noticeable results.

METHODS EMPLOYED IN ESTIMATING BLOOD CONTENT, BLOOD VOLUME AND SO FORTH

1 Circulating blood and plasma volumes were determined by the original dye method of Keith, Rowntree and Geraghty, vital red and Congo red being used interchangeably. In order to prevent coagulation, 1 c.c. of a 16 per cent solution of sodium oxalate was evaporated from centrifuge tubes, the oxalate being deposited uniformly in fine, powdered form on the inner surface of the tubes.¹⁴ In hematocrit determinations, three 10 c.c. standardized, graduated centrifuge tubes were used, the average or mean reading constituting the basis for calculating hematocrit values. In the colorimetric readings, the Duboscq colorimeter was used exclusively.

2 The water and solid contents of the blood were determined gravimetrically, before and after drying in vacuo over phosphorus pent-oxide at room temperature. Drying was continued until the weight became constant. Duplicate estimations were made in every instance, and average values taken. In the earlier stages of the work, specific gravity determinations were made by the pyknometric method, but these were subsequently discontinued, as they were not deemed essential.

3 The cell water calculations were made by means of the formula $x = \frac{A - (B \times C)}{D}$ in which A represents the percentage of water

¹⁴ With this technic, hemolysis rarely occurs.

in whole blood, B, the percentage of water in the plasma, C, the percentage of plasma by hematocrit, and D, the percentage of cells by hematocrit.

For hemoglobin determinations, the Palmei method was used. In several instances, the values thus obtained were checked with an acid hematin method devised by Osgood.

TABLE 2—*Table of Normal Values in Fifty Cases*

	Range	Average
Blood water, per cent	79 to 83	81
Plasma water, per cent	91 to 93	92
Cell water, per cent	60 to 68	64
Total circulating blood volume (according to the dye method), cc	4,930 to 7,430	6,180
Blood volume for each kilogram of body weight, cc	72 to 100*	86
Blood volume for each square meter surface area, cc†	2,550 to 4,010	3,360
Total circulating plasma volume (according to the dye method), cc	2,960 to 4,160	3,610
Plasma volume for each kilogram of body weight, cc	43 to 59	58
Plasma volume for each square meter of surface area, cc	1,420 to 2,250	2,050
Total circulating cell volume, cc	1,970 to 3,310	2,550
Hematocrit cells, per cent	38 to 45	41
Hemoglobin		
Author	Men, Determi- nations	Women, Gm for Each 100 C c
	61	14 14
Lichenstern	900	16 60
Williamson	12	13 80
Haldane and Smith		15 65
Haden (calculated on a red cell count of 5,000,000)		15 56

* Total volume values as high as 105 cc for each kilogram of body weight have been found in three normal controls. This group needs further study.

† Dreyer contends that blood volume is a function of surface area rather than body weight.

TABLE 3—*The Percentage Variation of Error Believed to be Inherent in the Different Methods*

	Per Cent		Per Cent
Blood volume	5 0	Cell water	2 0
Plasma volume	2 5	Hemoglobin	2 0
Blood water	0 5	Hematocrit	2 0
Plasma water	0 5		

The total circulating hemoglobin was determined from Haldane's¹⁵ normal value of 13.8 gm of hemoglobin for blood, with oxygen capacity of 18.5 per cent by volume. According to the following calculations, total percentage hemoglobin times 13.8 times total blood volume equals total circulating hemoglobin. The probable variations of error in methods employed may be noted in Table 3.

15 In this country, higher values have been obtained by Williamson and Haden (Table 2).

TABLE 4.—*Repeated Determinations of the Volume and Concentration of the Blood in Normal Persons*

Case	Date	Weight, kg	Hemo globin			Blood Volume, cc			Plasma Volume, cc			Water, per Cent			
			Total	Creatine, Gm	Hematocrit Cells, per Cent	Total	Each	Kg	Total	Each	Kg	Cell Volume, cc	Blood	Plasma	Cell
1	11/7/23	58	150	1,146	45	5,640	95	3,400	3,050	52	1,850	2,490	77.4	91.7	60.5
	11/9/23	58	132	976	43	5,840	83	3,250	3,050	53	1,850	2,290	80.2	92.6	63.7
2	11/7/23	51	114	777	40	4,930	96	3,170	2,060	58	1,910	1,970	80.1	91.6	62.8
	11/11/23	51	112	769	40	4,080	97	3,210	2,990	58	1,930	1,990	81.9	92.6	65.8
3	11/13/23	68	115	1,056	40	6,660	98	3,660	4,000	59	2,100	2,660	82.8	94.4	64.0
	11/15/23	68	113	1,005	43	6,440	94	3,540	3,670	54	2,020	2,770	80.3	92.6	64.0
4	11/30/23	60	114	837	38	5,820	88	3,160	3,000	54	1,910	2,020	80.3	91.9	66.4
	12/3/23	60	111	882	41	5,760	96	3,430	3,400	56	2,010	2,360	81.9	92.5	66.7
5*	12/1/23	72	115	935	43	5,900	82	3,120	3,360	46	1,780	2,510	79.8	92.2	63.2
	12/8/23	71	116	1,054	40	6,590	93	3,520	3,050	55	2,110	2,640	81.5	93.4	63.7
	12/15/23	70	103	928	40	6,590	91	3,580	3,950	56	2,120	2,610	83.0	93.2	67.5
6	12/3/23	68	109	1,028	41	6,850	100	3,610	4,010	59	2,230	2,810	80.5	91.6	63.7
	12/5/23	68	105	1,004	40	6,740	99	3,740	4,040	59	2,230	2,690	80.5	92.0	63.2
7	12/4/23	70	115	1,167	45	7,260	105	3,960	1,050	56	2,100	3,310	79.6	93.3	63.2
	12/7/23	70	116	1,183	44	7,470	106	4,010	1,160	59	2,250	3,270	80.4	93.2	64.0
8	12/6/23	80	113	1,114	44	7,140	89	2,550	4,000	50	1,425	3,140	80.0	92.3	64.0
	12/10/23	80	119	1,102	45	7,270	90	2,590	4,000	50	1,425	3,270	80.8	93.2	65.7
9	12/8/23	68	107	873	36	5,920	87	3,200	2,700	55	2,050	2,130	82.0	93.5	61.8
	12/10/23	68	107	929	38	6,310	92	3,130	3,010	57	2,110	2,400	82.3	93.5	64.0
10	12/12/23	71	122	901	42	5,370	75	3,020	3,100	43	1,750	2,240	81.3	94.2	63.5
	12/17/23	71	113	789	9	7,140	72	2,090	3,120	41	1,770	2,000	82.6	92.9	66.5
Average values		114		41	6,180	88	3,860	3,610	53	2,050	2,555	80.0	92.7	64.2	

* Dec 4, 1923 tonsillectomy.

NORMAL VALUES WITH METHODS EMPLOYED (TABLES 2 AND 4)

1. The circulating plasma volume in normal persons, as determined by the dye method, varies from 43 to 59 cc, the average being 53 cc for each kilogram of body weight. There is fairly marked constancy in plasma volume in health. In obese persons, as has been shown,¹⁶ the plasma volume is relatively lower.

2. In normal persons the relation of circulating blood volume to body weight varies from 72 to 100 cc, with an average of 86 cc for each kilogram of body weight.

3. The blood water, according to Mullej, averages 79.11 per cent in men, with a variation of ± 1 per cent. In women, the average value is 81.01 per cent with a variation of ± 1 per cent. In our normal cases the results agreed closely with these values. We believe that slight variations cannot be regarded as abnormal, a 1 to 2 per cent fluctuation in the blood water concentration being observed during the course of a day in normal persons. We are arbitrarily increasing the limits of normal variation, the normal range being considered to be between 79 and 83 per cent for men and women.¹⁷

16 Brown, G. E., and Keith, N. M. Blood and Plasma Volume in Obesity, Arch Int Med 33: 217-223 (Feb 15) 1924.

17 The maximal variation in thirty hematocrit estimations, using the three large tube method, was 2 per cent. The average variation was 0.7 per cent.

4 The plasma water in men and women, according to our data, varies from 91 to 93 per cent, the average being 92.5 per cent. Calculations on the same person at different periods show a fluctuation as high as from 1 to 2 per cent.

5 The cell water, as determined by centrifugating and drying is, according to Biermacht, between 70 and 72 per cent. Bic and Muller estimate 65.4 per cent for men and 64.81 per cent for women, and Schmidt estimates 68.8 per cent for a man, aged 25.¹⁸ The drying method may be open to criticism, but we find that the calculation-hematocrit method yields values closely approximating those quoted. We find that the normal cell water varies from 60 to 68 per cent. The average in fourteen calculations was 64 per cent. A variation of 6 per cent in the normal person during the day was observed.

6 The hematocrit values ranged from 38 to 45 per cent for the cells, and from 55 to 62 per cent for the plasma. The average for both men and women was 60 per cent plasma and 40 per cent cells. A daily variation of 2 per cent is observed in normal persons.

7 The normal standard of hemoglobin is as yet unsettled, this is somewhat surprising in a substance so important. Table 2 presents some of the different hemoglobin values accepted as normal by various investigators.

VOLUME STATES IN EDEMA

In order to contrast the magnitude of the changes in blood volume and composition in normal persons with that in patients with edema and those who have had diuresis, repeated determinations of blood and plasma volume, and of the water content of blood, plasma and red cells, have been made on a group of fourteen persons. The period between the determinations has varied from two to fourteen days.

One is wont to regard the blood changes associated with edema and diuresis as due merely to the addition or withdrawal of water. It seems to us that this position is untenable, and that it is necessary to take into consideration changes in volume of the blood, plasma and cells, hemoglobin and protein. In this study we are attempting to analyze the various changes and to present what appear to us plausible explanations of the phenomena encountered. We realize that we are inviting criticism, but believe that the importance of the subject justifies our attempt.

Before entering into the actual analysis of the results of our studies, it is necessary to enumerate the processes which are probably involved in changes in the volume of plasma and cells and their composition.

¹⁸ We recognize the sex differences in the blood water concentration, due to lower content of hemoglobin in females, but believe these variations are so slight as to be negligible in this study.

Obviously there may be (1) addition or withdrawal of water, of plasma, and of cells, (2) addition or withdrawal of solids of plasma and cells, and (3) the addition or withdrawal of plasma, or cells as such. The process consists, then, in the dilution or concentration of cells and plasma, which affects composition and volume, or the addition or withdrawal of blood, which affects volume chiefly. The processes encountered are complex, and probably involve changes in water, solids, volume of blood, and plasma and cells in varying degrees in different forms of edema.

It has been quite generally believed that a large blood volume with a decreased cell plasma volume ratio, oligocytemic hypervolemia, or a dilution state, exists in certain cases of edema. This conclusion was reached by observations on the erythrocyte and hemoglobin content of the blood, or the plasma protein content. Deductions concerning blood volume obtained by such a method are open to serious objection, as fluctuations in percentage values for blood cells and other blood solids do not necessarily reflect volume fluctuation. Neither does the plasma protein content bear any fixed relation to plasma volume, and changes in plasma protein may denote either actual quantitative or relative fluctuation in protein or water content. It would seem, therefore, that more accurate quantitative data should be assembled in individual instances, and that conclusions relative to volume changes should not be based solely on changes in concentration of blood or plasma.

This study, therefore, presents certain volume data obtained by the dye method and, we believe, throws new light on the blood state in edema. In the four types of edema studied, increased circulating volume, or hypervolemia, is found in four cases (Cases 1, 2, 6 and 14, Tables 5 and 6). These were instances of simple hypervolemia, as the normal cell plasma volume ratio was not disturbed except in one instance (Case 14), in which chronic anemia was present, oligocytemic hypervolemia. It is difficult to determine whether the increased blood volume represented a state of dilution or actual anemia. The accumulation of water in the blood sufficient to produce a maintained oligocytemic hypervolemia or a relative anemia is, on theoretic grounds, improbable. Dilution, if it occurs, is probably transitory and of short duration, as was shown in experimental cardiac edema by Bolton, and after forced water ingestion, by Greene and Rowntree. The blood, like the other tissues and organs of the body, is provided with a mechanism safeguarding against excessive fluid accumulations. When elimination by the kidney is blocked, the tissues take up the excess water from the blood. In this respect, edema can be considered a protective phenomenon. The serous cavities and the intestines, under stress, also provide safety outlets. When the blood volume is increased by the addition of water, physiologic mechanisms, if available, tend to reestablish

TABLE 5—*Total Circulating Volume and Water of the Blood in Edema and Postedema Periods**

Case	Diagnosis	Date	Hemoglobin			Circulating Volume, G. ^e			Total Water, C. ^e		
			Weight, Kg	Edema	Per Cent	Total Circu- lating Gm.	Blood	Plasma	Cell	Blood	Plasma
1	Mitral endocarditis with myocardial insufficiency	6/ 1/22	75.5	4	90	830	4,000	2,610	5,780	3,900	1,900
2	Mitral endocarditis with myocardial insufficiency	6/19/22	64.5	0	104	1,085	7,650	4,445	3,210	6,240	4,060
3	Hypertension, myocardial insufficiency, obesity	7/19/22	68.0	3	106	915	6,250	3,830	4,450	5,290	3,620
4	Diabetes mellitus	8/16/22	54.0	0	86	700	6,430	3,733	2,700	5,450	3,500
5	Diabetes mellitus	2/12/22	108.0	3	100	820	5,940	3,565	2,376	5,000	3,850
6	Diabetes mellitus	2/23/22	92.0	1	92	650	5,380	3,370	2,010	4,580	3,240
7	Subacute glomerular nephritis	8/17/22	74.5	2	105	835	6,820	3,055	1,860	4,820	3,600
8	Subacute glomerular nephritis	8/22/22	69.5	0	108	880	5,930	3,960	1,970	4,950	3,730
9	Subacute glomerular nephritis	8/22/22	83.0	3	132	1,090	6,000	3,600	2,400	4,680	3,350
10	Subacute glomerular nephritis	5/10/22	70.0	0	90	795	6,420	4,490	1,920	5,450	4,090
11	Subacute glomerular nephritis	9/24/22	91.0	2	120	1,125	6,900	4,285	2,510	5,470	3,940
12	Subacute glomerular nephritis	10/ 8/22	63.0	0	104	825	5,740	3,673	2,060	4,660	3,400
13	Subacute glomerular nephritis	9/30/22	58.0	3	69	330	3,620	2,500	1,120	3,120	2,340
14	Nephrosis, chronic osteomyelitis	10/20/22	61.0	1	63	300	3,520	2,650	870	3,050	2,470
15		8/ 7/22	91.0	4	82	460	4,380	3,335	1,050	3,790	3,150
16		9/11/22	68.0	0	89	500	4,100	2,926	1,170	3,570	2,750
17		6/ 1/23	65.0	3	40	220	4,050	3,605	440	3,600	3,320
18		7/ 3/23	56.5	1	52	235	3,300	2,640	640	2,800	2,420
19		11/15/22	61.0	3	80	330	3,050	2,285	700	2,120	2,100
20		1/ 5/23	48.0	0	51	220	3,200	2,600	600	2,820	2,450
21		9/26/23	52.0	0	100	480	4,610	2,910	1,700	4,000	2,720
22		10/ 1/23	84.0	2	128	1,170	6,650	3,674	3,000	5,310	3,440
23		10/23/23	74.0	0	124	1,130	6,620	3,710	2,910	5,370	3,490
24		10/ 7/22	94.0	4	119	1,120	6,830	4,235	2,590	5,630	3,950
25		11/29/22	86.0	2	84	780	6,720	4,235	2,480	5,670	3,990
26		2/20/23	83.0	3	113	1,090	7,010	4,135	2,870	5,700	3,910
27		5/16/23	75.0	0	115	1,050	6,860	4,119	2,710	5,400	3,800
28		5/18/23	65.0	3	91	710	6,010	4,571	1,440	5,030	4,140
29		8/31/23	56.0	0	95	702	5,400	4,150	1,250	4,640	3,930

* According to the dye method for estimating blood volume

Table 6.—Relative Volumes and Concentration of the Blood in Edema and Postedema Periods*

Case	Diagnosis	Date	Idein [†]	Hemo- crit Cells per Cent	Wt. Blood, Prism, per Cent	Crenating [‡] Volume, Cc for 1ach Kg		Relative Volume State, New Nomenclature
						Cell, per Cent	Blood Per Cent	
1	Mitral endocarditis with myocardial insufficiency	6/ 1/ 23	1	10	86.3	95.3	73.0	Hypervolemia simplex
2	Mitral endocarditis with myocardial insufficiency	6/ 9/ 23	0	101	91.6	91.1	69.0	Hypervolemia simplex
3	Hypertension myocardial insufficiency, obesity	7/19/23	3	106	91.9	81.3	69.0	Hypervolemia simplex
4	Diabetes mellitus	8/16/23	0	86	91.5	81.5	69.7	Hypervolemia simplex
5	Diabetes mellitus	8/19/23	1	100	91.0	81.7	71.1	Hypervolemia simplex
6	Diabetes mellitus	2/12/23	0	100	91.0	81.3	91.6	Hypovolemia simplex
7	Subacute glomerular nephritis	2/23/23	0	92	97	95.5	70.0	Hypovolemia simplex
8	Subacute glomerular nephritis	3/17/23	0	105	92.2	93.6	63.0	Oligoeythemic normovolemia
9	Subacute glomerular nephritis	3/23/23	0	109	92.7	92.9	62.0	Oligoeythemic normovolemia
10	Subacute glomerular nephritis Tonsillectomy	4/10/23	1	102	90.0	73.0	55.0	Normovolemia simplex
11	Subacute nephrosis	5/ 1/ 23	0	99	90.0	87.0	51.0	Oligoeythemic normovolemia
12	Subacute nephrosis	5/ 2/ 23	0	100	90.5	92.3	63.0	Hypovolemia simplex
13	Subacute nephrosis	5/ 9/ 23	0	100	90.5	92.1	60.0	Hypovolemia simplex
14	Nephrosis, chronic osteomyelitis	5/16/23	0	109	90.5	92.0	60.0	Hypovolemia simplex
		5/18/23	3	91	91.0	91.8	61.0	Normovolemia simplex
		5/21/23	0	95	91.0	91.8	60.0	Oligoeythemic hypovolemia

* According to the dye method for estimating blood volume.

† Calculated on the basis of body weight of the postedema period.

‡ Calculating blood volume

lish the normal cell plasma volume ratio, either by getting rid of water or by adding erythrocytes and hemoglobin, as shown experimentally by Bolton. The latter may have taken place in Cases 1 and 2 of the cardiac group. If these measures fail, a maintained or chronic oligocythemic hypervolemia or anemia would exist theoretically, as in edema superimposed on preexisting anemia. Case 14 may be an example of this type. In the majority of cases of chronic anemia, either normal or decreased total blood volume values exist according to the dye method, with a decreased cell plasma volume ratio (oligocythemic normovolemia, or oligocythemic hypovolemia), oligocythemic hypervolemia has been found more rarely. In Case 1, during the period of edema, there was simple hypervolemia, which became more marked following diuresis, the cell plasma volume ratio remaining normal. In Case 2, likewise, a simple hypervolemia was present during the edema period which was maintained during diuresis, although some actual loss of hemoglobin occurred. It would appear that diuresis, per se, played only a minor part in these two cases in modifying the abnormal volume state, once it was established (Table 6). One has to admit the possibility that hypervolemia may precede the development of edema in some forms of cardiac disease.

In order to determine whether there is dilution of the blood, repeated volume and hemoglobin determinations are necessary. Lacking the volume and composition data for the period preceding, it is impossible to determine from a single examination whether a dilution state exists in the edema period. Degrees of dilution sufficient to produce a relative anemia would be suspected in the presence of an oligocythemic hypervolemia. The subsequent determinations would reveal the constancy or inconstancy of the volume and hemoglobin values. If these are inconstant, the degrees of dilution or concentration accompanying diuresis may be revealed by a comparison of percentage change in the actual and in the percentage hemoglobin. (When the percentage hemoglobin shows a greater percentage fluctuation than the actual circulating hemoglobin, a dilution or concentration process may be suggested.) When the percentage hemoglobin shows a greater percentage reduction than the actual hemoglobin, an increase in total blood volume will probably be found, or, when the percentage hemoglobin shows a greater percentage increase than the actual hemoglobin, it may be explained by volume decrease. In the study of the water exchange in edema, many variations in the volume-water-solid factors are found. Simple adjustments are rarely encountered, complex adjustments involving all three of the variables are the rule.

In Cases 7, 8 and 10, of glomerular nephritis, decreased total blood volume with decreased cell plasma volume ratio, or oligocythemic hypo-

volemia, existed in both the edema and nonedema periods. In Case 9, there was a borderline normovolemia in the edema period, this is an interesting observation, since it agrees with our previous studies on the anemia of chronic glomerular nephritis, which demonstrate that anemia is an integral part of this disease. We believed that the conditions would probably be the same in the more acute forms of this type of nephritis, the results of the present study confirm this, and apparently prove that a state of dilution is not instrumental in causing the anemia of glomerular nephritis. Such a deduction might be expected on *a priori* grounds because of the marked avidity with which the tissues take up water in this disease. The experimental work of McClure and Aldrich¹⁹ is further proof of this "tissue thirst." The existence of anemia explains the high percentage of blood water found in certain types of nephritis, and has probably given rise to the conception of "hydremic condition of the blood." The volume changes in this group during diuresis were practically negligible, except in Case 9, in which there was a decrease in plasma volume and an increase of actual hemoglobin, apparently indicating a partial recovery from the anemia.

In Case 3 (cardiac edema in an obese woman), the relative blood and plasma volumes were low, which can be explained on the basis of obesity. In this case there was an actual reduction in cell volume and circulating hemoglobin during diuresis. The ratio of actual and percentage hemoglobin change was the same, showing that dilution played no part in the decrease of percentage hemoglobin. Normal volume states or normovolemia, predominated in the cases of diabetes and nephrosis, both in the edema and nonedema periods. In uncomplicated cases of nephrosis, there apparently was no anemia, which finding may be of importance in the differential diagnosis of nephrosis and glomerular nephritis. It has been observed, however, that in many of the cases of so-called nephrosis, there eventually is increased blood pressure and other evidence of involvement of glomerular function.

VOLUME CHANGES FOLLOWING DIURESIS

In Cases 1, 6 and 9, volume changes were noted following loss of fluid (Table 7). In Case 1 (cardiac edema), there was an increase of 950 cc in total blood volume, 350 cc in plasma and 600 cc in cell volume. This was not a dilution process, since the cell plasma volume ratio tended to increase. In Case 6 (diabetic edema), simple hypervolemia was present in the edema period similar to that observed in Cases 1 and 2 in the cardiac group. Following diuresis, the blood volume decreased 1,050 cc, a decrease of 600 cc in plasma, and 450 cc

19 McClure, W. B., and Aldrich, C. A. Time Required for Disappearance of Intradernally Injected Salt Solution J. A. M. A. 81: 293-294 (July 28) 1923.

in cell volume. The percentage hemoglobin decreased 13 per cent and the actual hemoglobin 26 per cent. This was a contraction process associated with both a water and actual hemoglobin decrease, with an excess loss of the latter. The percentage hemoglobin decrease was partially masked by a volume contraction, producing simple normovolemia. The normal cell plasma volume ratios were preserved. Only minor volume changes were noted during diuresis in all the cases of glomerular nephritis except Case 9, in which there was oligocythemic normovolemia in the edema period, during diuresis, the plasma volume decreased 970 c.c., whereas the cell volume increased 220 c.c., producing an oligocythemic hypovolemia, with a net decrease of 750 c.c. in the total blood volume. This may indicate a contraction mechanism, associated with an actual increase of circulating hemoglobin. This is an

TABLE 7.—*Absolute and Percentage Volume Changes During Diuresis**

Case	Type of Edema	Blood				Plasma				Cells			
		Increase		Decrease		Increase		Decrease		Increase		Decrease	
		C c	Per Cent	C c	Per Cent	C c	Per Cent	C c	Per Cent	C c	Per Cent	C c	Per Cent
1	Cardiac	950	14.0			350	8			600	24		
2	Cardiac	150	2.5					100	3	250	10		
3	Cardiae			560	9			180	5			860	15
4	Diabetic	120	3.0				No change			110	6		
5	Diabetic	420	7.0			900	25					470	20
6	Diabetic			1,060	15			610	14			450	17
7	Glomerular nephritis			100	3	150	6					250	20
8	Glomerular nephritis			280	6			410	2	120	12		
9	Glomerular nephritis			750	19			960	27	210	48		
10	Glomerular nephritis	150	5.0			310	14					160	21
11	Nephrosis			No change			No change				No change		
12	Nephrosis			110	1.5		No change					110	4
13	Nephrosis			140	2		No change					130	5
14	Nephrosis			610	10		420	9				190	14

* As calculated by the dye method.

interesting phenomenon, possibly revealing a recovery from anemia accomplished in two ways, by a contraction of the blood volume, and by an actual increase of the circulating hemoglobin. The blood volume shrinkage may be the result of an excessive plasma water removal, incident to diuresis, or it may be a natural compensatory process, having as its object a greater increase of percentage hemoglobin. In Case 5 (diabetic edema), there were simple normovolemia and abnormally high percentage hemoglobin, revealing increased blood concentration. Following a loss of 13 kg of body weight, the plasma volume increased 900 c.c., the cell volume decreased 480 c.c., and there was a marked decrease in the cell plasma volume ratio by hematocrit, thus producing oligocythemic normovolemia. There was an actual loss of circulating hemoglobin of 300 gm (27 per cent), and a 32 per cent decrease in percentage hemoglobin, revealing the production of a true anemia, with mild dilution of the blood. The cases of nephrosis (Cases 11, 12 and 13) revealed only minor volume fluctuations during the period of fluid

loss. In Case 14 (nephrosis with moderate anemia), there was a loss of 610 cc in total blood volume, 420 cc in plasma, and 190 cc in cell volume, indicating a progressive anemia associated with water loss. The volume contraction concealed the loss in actual hemoglobin, the percentage hemoglobin showing no change.

STUDIES ON BLOOD AND PLASMA COMPOSITION IN RELATION TO BLOOD CONCENTRATION (TABLES 3 AND 5)

The blood and cell water percentage in the edema period were variable, and bore a close relation to the hemoglobin content, rather than to the volume. The highest percentage of blood water, as would be expected because of the anemia, was found in the cases of glomerular nephritis. In a case of diabetic edema (Case 5) a moderate concentration of the blood and cells existed during the period of edema; following diuresis, a marked increase or restoration in the percentage water of the blood and cells took place, while the percentage plasma water decreased 1 per cent. In Case 13, following diuresis, a definite dehydration occurred in the cells and plasma.

In nine of the cardiac and renal cases (Cases 1, 2, 3, 8, 10, 11, 12, 13 and 14), the plasma water was relatively increased either in the edema or postedema period, showing the existence of hydremia. This was as infrequent, however, in the dry as in the edema period. In Cases 1 and 14, the plasma volumes were increased, but, as the plasma proteins were not determined, it is not known whether there was an actual protein loss or a dilution. In the other cases the relative plasma volumes were normal. Since hydremia was more common in hypovolemic than in hypervolemic states, it is evident that the percentage plasma water gives no information as to the circulating blood or plasma volume. In Case 13, a definite decrease in plasma water took place during diuresis, but no change in relative or absolute plasma volumes.

As a result of diuresis, the plasma water content varied slightly in all but one case (Case 12). The greatest fluctuations were observed in Case 1 (cardiac edema) and in Case 13 (nephrosis). In Case 1 there was a marked decrease in percentage plasma water with an increase in absolute blood and plasma volume. In Case 13, in which there was a plasma water decrease, no change occurred in plasma volume. In Cases 5, 6 and 9, in which the greatest plasma volume changes occurred with fluid loss, only slight changes occurred in plasma concentration.

The percentage cell water, according to the calculation hematocrit method, reveals great fluctuations. In Case 5, following fluid loss, a 13 per cent increase in cell water, and a 32 per cent decrease in hemoglobin were observed.

The percentage hemoglobin showed no constant value during edema except in cases of glomerular nephritis. The hemoglobin fluctuations during diuresis were not constant for any of the edemas. Considerable fluctuations in either direction were observed. In several cases, however, the hemoglobin revealed no change during diuresis.

The percentage hemoglobin changes were roughly proportionate to those of the cell volume, but not to those of the total volume. In Case 5, during diuresis, there was a 32 per cent decrease in percentage hemoglobin, but the total blood volume increased only 9 per cent. The increase in plasma volume explains this disproportion.

In Case 2, a definite decrease of hemoglobin occurred, with a slight increase in total blood and cell volume. This finding is difficult to explain, however, the volume changes were not much greater than the possible error of the method used in their determination. In the majority of the cases in which the percentage hemoglobin did not change during the period of fluid loss, volume changes were slight or nil. The greatest fluctuations in either direction in percentage hemoglobin took place in the cardiac and diabetic edemas. The fluctuations in percentage hemoglobin do not accurately reflect the fluctuations in total blood volume (Cases 2, 5 and 8, Table 5). The fluctuations in plasma volume may entirely mask those of the cell volume. In Case 13 there was a loss in circulating hemoglobin of 8 per cent, with no change in percentage hemoglobin, the discrepancy being explained by a 10 per cent decrease in the total blood volume.

COMMENT

The blood volume states in the small number of cases of edema in this series reveal a tendency to grouping of the different clinical types of edema. It should be recognized that the accuracy of the values relative to volume depend on the validity of the findings by the dye method. Simple hypervolemia predominated in the cardiac cases and in one case of diabetes in the edema stage. Hypovolemia was practically constant in the cases of glomerular nephritis, while normovolemia was the rule in the cases of nephrosis and diabetes. There is no absolute evidence that sufficient dilution occurred in the period of edema to produce oligocytemic hypervolemia, or to cause a relative or dilution anemia except, possibly, in one case of nephrosis complicated with chronic infection of bone (Case 14). Dilution processes in minor degrees were found in several instances following diuresis, apparently representing adjustments in the volume water solid balance following fluid loss. Oligocytemic hypervolemia is probably rare, and may represent a dilution condition resulting when the physiologic mechanisms fail to maintain the normal cell plasma volume ratio in the presence of an excess of blood water.

The blood was decreased in relation to body weight in the presence of obesity, and this relationship was maintained in the presence of edema in one case. The hypovolemia in cases of edema of glomerular nephritis is explained on the basis of anemia or decreased cell volume. The cell plasma volume relationship showed a tendency to maintain the normal ratio in the cases of cardiac disorders, diabetes and nephrosis, in both edema and nonedema periods. When this ratio was not maintained, anemia was present. Anemia is practically always associated with glomerular nephritis,²⁰ and therefore there was a decrease in cell plasma volume ratio in these cases, both in edema and nonedema periods. There was no evidence that dilution played a part in the anemia of glomerular nephritis. There were no uniform changes in the volume states during diuresis in the various types of edema. In the renal cases minor fluctuations, if any, were observed in cell and plasma volumes. The greatest fluctuations were observed in the cardiac and diabetic cases. Changes took place in either direction, indicating volume contraction, mild dilution, or restoration and concentration processes.

The concentration values during the edema period were too variable to permit generalizations. Hydremia, or increased water content of the plasma, was found occasionally in all types of edema, in periods of edema and in periods free from edema. The highest concentration value was found in cardiac cases. No constant fluctuation occurred during the period of diuresis, and the changes were not uniform, occurring in either direction.

The cell water percentage fluctuated widely, which possibly explains the slight variations observed in the cell percentage by hematocrit. The fluctuations in percentage hemoglobin do not always reflect changes in the total blood volume, as plasma volume variation may partially mask the fluctuation in actual hemoglobin and cell volume.

SUMMARY

In a small series of cases representing different types of edema, the blood was studied in relation to the circulating total blood and plasma volume and its composition in both edema and postedema periods.

Because of the confusion and inadequacy of terms relating to volume states, certain new terms are proposed. In the edema stage, an increased total circulating blood volume, simple hypervolemia was observed in certain of the cardiac and diabetic cases, but not in any case of edema of renal origin. No definite evidence was obtained to show that oligocytemic hypervolemia exists as a maintained state in edema, except possibly in the presence of a true anemia. A decreased blood volume

²⁰ Brown, G. E., and Roth, Grace M. The Anemia of Chronic Nephritis, Arch. Int. Med. **30** 817-840 (Dec.) 1922.

with a decreased cell to plasma volume ratio, oligocythemic hypovolemia, was found in the four cases of glomerular nephritis. This is explained on the basis of the existing anemia, and apparently stands in no relation to the edema itself. The anemia is a true or absolute anemia and is not due to dilution. Simple normovolemia was found in all three uncomplicated cases of nephrosis.

Studies of the composition of the blood revealed no fixed relationship between hydremia (increased percentage plasma water) and the volume state. Diuresis exerts no fixed influence on the volume and composition of the blood. Only minor changes characterize the disappearance of edema of renal origin and are probably, in some instances, related to compensatory efforts of the blood to establish normal cell plasma volume ratios. The cases of renal edema show the least fluctuation during diuresis.

During diuresis, marked changes in blood volume were observed in certain cases of edema of cardiac or diabetic origin, representing variable adjustments in volume, solids and fluid factors. In diuresis the percentage fluctuation in any one constituent of the blood does not necessarily reflect corresponding volume changes. Changes in blood solids may be partially or completely masked by fluctuation in water content in the absence of volume changes.

Book Reviews

MANAGEMENT OF DIABETES By GEORGE A HARROP, JR Pp 176 Price, \$2.00
New York Paul B Hoeber, 1924

Since insulin has become important in the treatment of diabetes, a manual containing instructions in directing its use, along with dietary regulations, is needed by the general practitioner. Such information, given with sufficient detail, is contained in this book by Harrop.

There are discussed the metabolic derangement in diabetes, the acid base mechanism and the acidosis of diabetes, insulin and its physiologic effects in the body, the management of the diabetic patient with insulin and diet regulation, and the treatment of acidosis, as well as other complications of diabetes.

The instructions regarding diet regulation include useful recipes and food value tables. Methods are given for determining the alkali reserve and sugar of the blood, as well as qualitative and quantitative tests for sugar and other urine constituents.

The text is a useful guide for the general practitioner, and may be given for instruction to intelligent patients.

CLINICAL LABORATORY DIAGNOSIS By ROGER SYLVESTER MORRIS Pp 456,
5 plates, 99 illustrations New York. D Appleton & Co, 1923

This is an excellent, well illustrated text for clinical laboratory examinations, considerably more extensive than the 1913 volume. It contains detailed instructions for conducting qualitative and quantitative examinations of the dissolved urine constituents, as well as for the identification of the formed elements. The same is true as regards examinations of the gastric juice, the feces and the sputum. Much useful information regarding the identification of parasites, both vegetable and animal, is included. Bacteriologic methods for identifying organisms of the mouth, eye, throat and nose are given, as well as those necessary for recognizing the vegetable and animal parasites of the skin.

The chapter dealing with blood examinations contains instructions for determining the cell content, the hemoglobin and certain ratios, such as the volume and color indexes, the viscosity, the coagulation time, the specific gravity and the fragility of red cells. The instructions for identifying the cells in stained preparations are complete. There are given descriptions of the changes in the blood with different diseases and the identification of blood parasites. The culturing of the blood for bacteria, and directions for determining, quantitatively, the chemical constituents are included. There are other instructions for examining spinal fluid and fluids from serous cavities.

This is a well organized and useful laboratory manual.

QUESTIONS ACTUELLES DE BIOLOGIE MÉDICALE Par G H ROGER, Doyen de la Faculté de médecine de Paris, Professeur de Pathologie expérimentale et comparée, Membre de l'Académie de Médecine Paris Masson et Cie, 1924

This monograph is essentially a summary of the author's own researches on the lungs, the cardiovascular system, the suprarenals, the liver, the ferments and the bile. Each of these subjects is treated in a separate chapter. The author has made special investigations on the action of the lung on the fatty substances of the blood, and concludes that the lung tissues have a very marked lipolytic action.

The chapter on cardiovascular physiology and pathology deals particularly with experiments with injections of organ extracts.

In the chapter on the suprarenal glands, the author details experiments which lead him to conclude that the suprarenal medulla secretes epinephrin continuously in quantities sufficient to counterbalance the influence of the vagi nerves on the heart

In the chapter on the rôle of the bile, the author concludes among other things, that bile retards intestinal putrefaction by three processes that is, it favors the development of *B. coli* and depresses the development of anaerobic organisms, it diminishes the secretion of ferments by the bacteria, and it decreases the action of these bacterial ferments on fermentable material

There are very few references to the literature in the monograph, and no index

APERCU DE LA PHYSIOLOGIE ET DE LA PATHOLOGIE GENERALES DU SYSTEME LACUNAIRE Par C ACHARD, Professor de clinique medicale a la Faculte de medecine de Paris, Membre de l'Academie de medecine Pp 125 Paris Masson et Cie, 1924

This monograph is a critical and useful review of the physiology and pathology of what the author calls, the "systeme lacunaire." Under this term, the author includes the great variety of spaces in the body, such as the intercellular spaces, the lymph spaces in the connective tissues, the subarachnoid spaces, the spaces in the internal ear containing endolymph and perilymph, the spaces in the eye containing the aqueous and vitreous humor, the serous cavities of the body, and the spaces in the joints containing synovial fluids, as well as the fluids in these varieties of spaces, and the physiology of the modification of these fluids in diseases such as edema, glaucoma, hydrocephalus and inflammations. The author points out the primitive character of this system of tissue spaces, this system antedating, both in phylogeny and autogeny, the vascular and the true lymphatic systems.

In the last chapter, the author discusses the therapeutic measures for the control of the various types of edema and excess accumulation of fluids in the lacunaire systeme.

The appendix contains analyses of the chemical composition of all these various fluids in health, and in many cases as modified by various diseases.

The literature cited is mainly French and German. The author refers to only two English and twelve American contributions in this field. Research men and internists interested in the fundamental problems of hydration, dehydration, edema, etc., will find the volume interesting and helpful.

DISEASES OF THE CHEST AND PRINCIPLES OF PHYSICAL DIAGNOSIS By GEORGE W NORRIS, M D, Professor of Clinical Medicine in the University of Pennsylvania, and HENRY R M LANDIS, M D, Director of the Clinical and Sociological Departments of the Henry Phipps Institute of the University of Pennsylvania. With a chapter on the Electrocardiograph in Heart Disease, by EDWARD KRUMBHAR, PH D, M D, Director of Laboratories of the Philadelphia General Hospital Cloth Price, \$9.50 net Third edition, revised Pp 907, 432 illustrations Philadelphia W B Saunders Company, 1924

The third edition has been revised and enlarged. It is a book of 907 pages, attractively printed and adequately illustrated. Some parts have been rewritten and the descriptions of a number of rare conditions, formerly omitted, are included. The work is too well known among medical educators to require detailed description. The numerous illustrations of frozen sections of the normal and of the grossly pathologic chest, showing the relationship of deep structures as well as of surface anatomy, are especially valuable. The chapter on the electrocardiograph is a clear and concise presentation without undue emphasis on this rather technical phase of physical diagnosis. In fact, the importance

of established means of physical diagnosis as compared with modern laboratory methods, without, however, detracting from the usefulness of the latter, is stressed throughout the book.

Parts I and II are concerned with the examination, and Parts III and IV with diseases of the respiratory and circulatory systems, respectively. Since the special parts include etiology, bacteriology, morbid anatomy, and symptomatology of diseases of the chest, the scope of the work necessarily overlaps the fields both of physical diagnosis and general medicine. The book is among the best texts in English on diseases of the chest, it is chiefly of value, however, as a text on physical diagnosis. That there is a demand for a book of this type is evidenced by the fact that it has gone through three editions in seven years. Practitioners of medicine undoubtedly find it a useful treatise on diseases of the chest.

From the standpoint of the medical student, the book does not meet the requirements of an ideal text on physical diagnosis. It is not possible for him to use the present volume exclusively, even in its restricted field. For example, about two-thirds of the present volume, i.e., Parts III and IV, deal with the principles of medicine—etiology, pathology, symptomatology, etc.—as restricted to diseases of the chest. Much of the material would be better covered in a general text on the principles and practice of medicine. Moreover, physical diagnosis as applied to the head, abdomen and extremities is not included. While these are admittedly of less importance, an ideal text for students should include them.

The idea suggests itself that it would be a valuable contribution to medical education in this country if future editions of this excellent work could be restricted to the field of physical diagnosis, without necessarily shortening it. The ideal text in English on physical diagnosis remains to be written.

LECTURES ON ENDOCRINOLOGY By WALTER TIMME, M.D., Attending Neurologist, Neurological Institute, New York, Professor of Endocrinology, Broad Street Hospital, Professor of Nervous and Mental Diseases, Polyclinic Medical School and Hospital Price, \$1.50 Pp 123, 27 illustrations New York Paul B Hoeber, 1924

This little booklet is a reprint of an article published, in 1921, in the *Neurological Bulletin*. It contains chapters on the thymus gland, the pineal gland, the thyroid gland, the suprarenal glands, the pituitary gland and the gonads, together with a small number of references to the literature (six pages), and a brief index. The diction is concise and clear, the illustrations (photographs of patients) are on the whole, well selected, but the author frequently fails to distinguish clearly between theories and facts. Perhaps this is not so easily done in treating of the difficult subject of endocrinology in such a brief space. Naturally, the author stresses particularly the nervous manifestations of ductless gland disorders, or alleged ductless gland disorders, not always clearly showing which is cause and which is effect. The author accepts, apparently *in toto*, the current theories of the "vagotonia" and "sympathicotonia." He states, "Theoretically, the thymus secretes a substance which has vagotonic properties, and practically this is frequently found to be borne out." So far from actually being found frequently or infrequently it is still an open question how or whether the thymus actually functions as an endocrine gland. Certainly the extirpation of the thymus, in young animals, gives no support to the endocrine function theory of the thymus. According to Timme, persons with precocious involution of the thymus "are themselves precocious, with much initiative, are easily aroused to anger, and are resentful. They have cruel instincts and show little inhibition. Although they seem far advanced for their years while still young, they never seem thoroughly to mature, and become blocked in early adolescence. They seem to retain their impulsive, unreasoning characteristics, brook no restraint, and remain con-

stantly a prey to their easily aroused anger." This seems a big indictment against the thymus, on the basis of what is actually known of the function of this gland, at present.

In the chapter on the thyroid gland, the author states that "ammonium carbonate is converted finally into urea by parathyroid action." But where is the evidence for this interesting statement? The author ascribes the symptoms of the normal and artificial menopause in women to hyperthyroidism. "A good example of such hyperthyroidism is that seen in some women after the menopause—the ovarian function having ceased, the thyroid is left without sufficient counterbalance and a hyperthyroid state ensues. This awakens overactivity of the adrenals, with resulting high blood pressure, and the combination produces the flushing, the vasomotor instability, the paresthesiae, etc., of this condition." The control or inhibition of the thyroid by the gonads is still an unproved assumption, and there is no reliable evidence that the nervous manifestations of the menopause are due, in whole or in part, to excessive activity of the thyroid. Certainly, castration or spaying in animals does not lead to hyperthyroid symptoms, if we can rely on the basal metabolism as an index of thyroid activity.

In the chapter on the suprarenals, the author assumes that excessive blood pressure or hypertension is caused by excessive activity of the suprarenal medulla, and that the function of the suprarenal cortex is that of inhibition, or regulation of the output of epinephrin by the medulla. These are interesting speculations of working hypotheses, but can hardly as yet be put out as conclusions to guide the practitioner in diagnosis and treatment.

In the chapter on the gonads, the author says, "During the period following menstruation when the corpora lutea are formed, there is usually a diminished thyroid activity. As this period of luteal activity begins to wane, and the next menstrual period approaches, the thyroid, presumably less opposed, becomes overactive and the nervousness, excitability and general mental uneasiness produced by thyroid activity become manifest." This assumption of thyroid hyperactivity and hypo-activity, in certain periods of the menstrual cycle, is not borne out by basal metabolism studies.

In the preface to the booklet, the author says he has in mind the production of a larger and more complete work on this subject. In this larger work contemplated, it is to be hoped that the author's facile expression and clear diction will be coupled with greater critical analysis, both of the clinical and the experimental data in this difficult field.

Archives of Internal Medicine

VOLUME 35

FEBRUARY, 1925

NUMBER 2

ARTERIAL HYPOTENSION *

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It is well at times to free our minds from the fixity of things as they are and try to see an object in its actual relationship to the complete scheme of things to which that object belongs. A true perspective thus gained will occasionally save us from getting too far from the main road of travel and from going astray.

Because arterial hypertension has been so widely studied, even to the point of having quite a number of books written on the subject, arterial hypotension has likewise been trotted into the medical arena, to have its action and values carefully rated.

Whatever advance has come to medicine through the study of arterial tension, this study was only made possible by the perfected sphygmomanometer. Blood pressure instruments, as well as blood pressure studies, have rendered a signal service to medicine, and we who have used them, each model in its turn, are grateful to Stanton, Nicholson, Faught and others for their efforts in simplifying and standardizing the sphygmomanometer, and making of it a practical every day instrument, and to Norris, Goodman, Gittings and others for their valuable contributions to the subject.

A noted internist examines a patient and evaluates his disease, and an average practitioner examines a similar patient and places his estimate on the case. It is easy to surmise that there will be two widely varying diagnoses as a result of different experiences and breadth of point of view. On the other hand, blood pressure estimations made by the same examiners of totally unequal medical skill will give the same result and have exactly the same scientific value.

One may therefore say that a procedure, no matter how limited its scope, which makes the effort of the most experienced, and that of the average physician of equal scientific value, is advantageous to medicine. Instruments of precision are democratizing the practice of medicine very rapidly. We need more instruments, more methods of precision, more criteria, and more standardization, but, above all, we need correct interpretation of the data furnished by these methods. Great clinical

* Read by invitation before the section on general medicine, College of Physicians of Philadelphia, April 28, 1924.

insight will ever remain the genius of a few. But of what good is the science of medicine if it does not reach all the sick in the time of their need?

Arterial tension of a certain height, however produced and maintained, is necessary for propulsion of the blood. Sir James Barr¹ has well said, "Without a certain diastolic pressure, man could not assume and maintain the erect posture. If you hang a rabbit by the ears, after the sympathetic nervous system has been divided in the neck, it immediately dies because all the blood gravitates into the abdomen. Only for the resistance created to the outflow, by the vasomotor nerves, man would have to go on all fours."

It is well then, since there is arterial tension, hypertension and hypotension, that we learn its full significance and what there is for us to do about it.

My discussion deals with arterial hypotension. For a more complete understanding and a broader view of the subject as a whole, I shall present for your consideration some observations on low blood pressure, both in health and disease. For the sake of uniformity with the work of others, I have adopted the level of 110 mm of mercury or less as indicating arterial hypotension. Having agreed that 110 mm of mercury is the high point of arterial hypotension, we may ask ourselves first of all, What is the frequency of hypotension in health? In answer to this, one should examine healthy groups to determine the incidence of this condition.

RESULTS OF EXAMINATIONS

Group 1—In 1914, at Carnegie Institute of Technology, Pittsburgh, we made a study² of blood pressures in 656 students. In this series, we found twenty-three cases in which the systolic pressure was from 100 to 110 mm of mercury, and seven in which the systolic pressure was from 90 to 100 mm of mercury. This made a total of thirty cases of hypotension in 656 normals, which was an incidence of about 4 per cent.

Group 2—In the summer of 1918, at Camp Sherman, out of a series of 31,596 recruits, 1,315 were referred to our cardiovascular board for special study. In this group of 1,315, there were seventy-three cases of pure arterial hypotension. This hypotension group did not include cases of any recognized cardiovascular or other organic disease. Of these seventy-three cases, we found it necessary to reject thirteen.

¹ Barr, James. High Arterial Pressure, Its Nature, Causes, Effects and Treatment, Am Med **29** 349 (June) 1923.

² Barach, J. H., and Marks, W. L. Blood Pressures, Their Relation to Each Other and to Physical Efficiency, Arch Int Med **13** 648-655 (April) 1914.

with the diagnosis of arterial hypotension, believing that those men were incapable of performing the duties of a soldier. The incidence of hypotension for the group was about 5.5 per cent.

Group 3—In this group of 27,224 recruits, 1,016 were examined by our board. Of these, twenty-four were rejected as in Group 2, an incidence of about 2.3 per cent.

Group 4—In the examination of last year's freshmen at the Carnegie Institute of Technology, Dr Wm L Marks and I² examined the records of 1,100 males. In this 1,100, we found that fifteen had a systolic pressure of 110 mm of mercury and nine had a systolic pressure

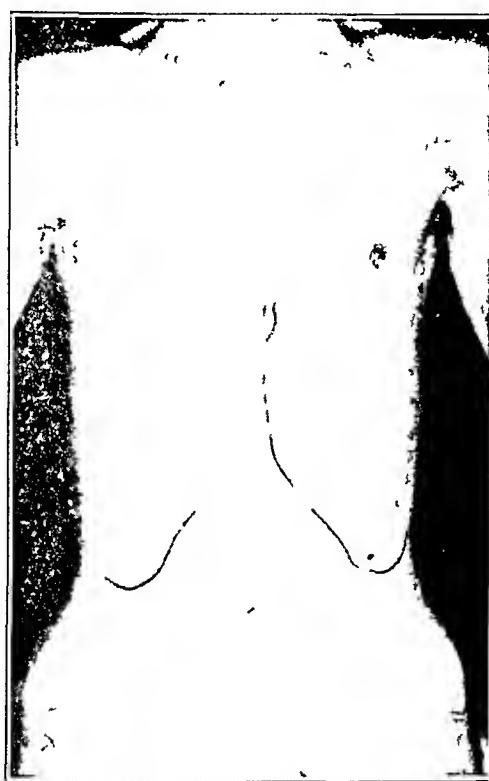


Fig 1.—Asthenic type, hypotension, 68 per cent

of less than 110 mm of mercury. Again, we find an incidence of about 2.5 per cent.

The body weight of these hypotension patients was considerably less than that of the other men. Compared to standard body weight, seventeen out of the twenty-four averaged 16 pounds (7.3 kg) under normal for their age and weight. Two were normal, and five out of the twenty-four were 5 pounds (2.3 kg) above normal. This underweight indicates the type of individual in whom hypotension occurs.

Another characteristic of the type is found in the chest expansion, which was 29 inches (72 cm) for the hypotension patients while it was 31 inches (78 cm) for the normals.



Fig 2—Sthenic type, hypotension, 97 per cent



Fig 3—Hypersthenic type

Group 5—I now present a group illustrating the physical efficiency of this type of case. In 1910, we made a study of fifty-five Marathon runners.³ There were three cases of hypotension. While all the contestants trained for a period of months prior to the race, we found that, in the three hypotension cases, one contestant dropped out within the first few miles of the race, another ran 10 miles and quit, and the third ran 13 miles and quit, showing the physical incapacity of these hypotension subjects. Two of these three were under normal weight. The losers as well as the hypotension subjects had smaller chest capacities than the winners. In rating the physical efficiency of the fifty-five contestants, the hypotension subjects were awarded forty-third, fiftieth and fifty-first place.

Gordon, Levine and Wilmaers⁴ recently reported their observations on a group of Marathon runners in Boston. In going over their figures pertaining to vital capacity, it is to be noted that with the height formula of Hewlett and Jackson as an index of vital capacity, the vital capacity of the first to finish the race was above normal. Subdivided in groups of ten, we note that the vital capacity of the first ten to finish the race was 106.7 per cent of normal. The second ten was 106.3 per cent of normal, the third was 104.3 per cent of normal. While the figures are not much above normal, they do indicate the tendency.

ANALYSIS OF RESULTS

Including the five groups, we see that arterial hypotension occurred in about 3.5 per cent of the 4,142 men of student and military age. Alvarez,⁵ in a group of 6,000 men students in California of the same ages as our students, reports an incidence of 2.2 per cent. We found hypotension subjects to be considerably under normal weight. Fisk⁶ of the Life Extension Institute noted underweight to be the predominant characteristic in 70 per cent of the hypotension subjects picked out of a group of 17,000 insurance risks. Symonds,⁷ reviewing a large group of 150,419 insurance risks, observed that lighter built groups have lower blood pressures than heavier ones. We found that hypotension

³ Barach, J. H. Physiological and Pathological Effects of Severe Exertion on the Circulatory and Renal System, Arch Int Med 5 382-405 (April) 1910
Savage, W. L., Boyce, J. W., and Barach, J. H. Physiological and Pathological Effects of Exertion, Am Physical and Education Rev 15, December, 1910, 16, January, February, March, April, May, 1911

⁴ Gordon, B., Levine, S. A., and Wilmaers, A. Observations on a Group of Marathon Runners With Special Reference to the Circulation, Arch Int Med 33 425 (April 15) 1924

⁵ Alvarez, W. C., Wulzen, R., and Mahoney, L. J. Blood Pressures, Arch Int Med 32 17 (July) 1923

⁶ Fisk, E. L. The Relationship of High Blood Pressures to Other Impairments, Am Med 29 446 (June) 1923

⁷ Symonds, B. Blood Pressure in Health (Mutual Life Insurance Company, New York) Am Med 29 408 (June) 1923

patients have a smaller chest capacity. Our observations also show that hypotension patients display a marked inefficiency for arduous and sustained physical effort, and that they are distinctly of the nonathletic type. In the Boston runners referred to, the vital capacity was smaller in the third group of ten, who finished last.

At this point, I wish to call attention to the observations of Larimore⁸ who made a study of a group of 417 male and female factory workers, whom he divided into four types—the sthenic, hypersthenic, hyposthenic and asthenic. Hypotension was present in 97 per cent of the sthenic males, and in 68 per cent of the asthenic males, in 18.8 per cent of the sthenic females, and in 64.5 per cent of the asthenic females.

We may therefore say that, among normals, hypotension occurs in lighter weight individuals of the hyposthenic and asthenic build having smaller chest capacity, and in those who are distinctly of the non-athletic type.

PHYSIOLOGIC VARIANTS PRODUCING LOWER ARTERIAL TENSION

It is well known that, on reaching high altitudes, a series of circulatory changes take place. There is adjustment and readjustment of the respiration and circulation. These changes are produced by lack of oxygen, the result of lowered partial pressure of oxygen.

Likewise, at any altitude, in a closed system, such as a breathing apparatus, or in a closed chamber, reduction of oxygen supply will bring on all the symptoms of altitude sickness—dizziness, visual disturbances, depression of the nervous system, cyanosis, weakness and exhaustion, headache, nausea, vomiting, thoracic oppression, rapid pulse, air hunger, a temporary rise and then a fall of blood pressure. These symptoms come on with varying rapidity, depending on the physical condition of the subject.

Along with these symptoms of altitude sickness, Greene and Gilbert⁹ have shown by numerous electrocardiographic studies that oxygen want produces a depression of cardiac function. Rhythm production and rhythm conduction both are interfered with when the oxygen supply falls to a certain level.

A fact well known, clinically, is that the sthenic, the broad chested, the athletic type of individual adjusts himself to oxygen want quite well,

⁸ Larimore, J. W. A Study of Blood Pressure in Relation to Types of Bodily Habitus, *Arch. Int. Med.* **31** 567 (April) 1923.

⁹ Greene, C. W., and Gilbert, N. C. Studies on the Responses of the Circulation to Low Oxygen Tension, III, Changes in the Pacemaker and in Conduction During Extreme Oxygen Want as Shown in the Human Electrocardiogram, *Arch. Int. Med.* **27** 517-557 (May) 1921, V, Stages in Loss of Function of the Rhythm Producing and Conducting Tissue of the Human Heart During Anoxemia, *Am. J. Physiol.* **56** 475 (July) 1921.

whereas the asthenic type, the hypotension type, stands it poorly. The first effect of the higher altitude on blood pressure is an increase. When readjustment has occurred, a sustained increase in pressure is never seen. When the observations have been satisfactorily made, there is either a distinct fall or a readjustment toward the normal.

The animal organism accommodates itself remarkably well to diminished oxygen. Lovenhart¹⁰ pointed out that if the atmospheric oxygen were reduced by half, animal life would not be interfered with noticeably, but that locomotives could not run, illuminating gas would not burn and many highly inflammable substances would be as inert as water.

HYPOTENSION IN DISEASES

Let us now turn to some observations on the occurrence of arterial hypotension in disease. Of these we will first consider our findings in the acute infectious diseases.

Typhoid Fever—In 1905, I made a series of observations on eighty-one cases of typhoid fever.¹¹ The readings were made four times daily throughout the course of the disease. Hypotension was found present from beginning to end, reaching its lowest level in the fourth week of the disease. The average systolic pressure for the entire group of eighty-one cases was 93 mm of mercury in the first week, 92 mm in the second week, 83 mm in the third week, 83 mm in the fourth week, 85 mm in the fifth week, and 90 mm in the sixth week of the disease. As convalescence progressed, pressure returned to normal.

Influenza—Influenza is the acute infectious disease of the northern temperate zone, in which the blood pressure seems to reach its lowest level. In September, 1918, I studied the blood pressure in a series of fifty cases of influenza at the Base Hospital, Mineola, L. I. For the entire group, the average systolic pressure was 89 mm, and the diastolic

Typical Blood Pressure Curve in Influenza

First Day	Second Day	Third Day	Fourth Day
115	92	85	112
70	60	60	70
72	60	72	72

pressure 53 mm of mercury. The lowest systolic pressure was 72 mm, and the diastolic pressure 48 mm of mercury. In uncomplicated cases, the pressure continued falling during the first, second and third day of the disease, and began rising on the fourth day. A typical curve is shown in the accompanying table.

10 Lovenhart, A. S. Certain Aspects of Biological Oxidation, Arch. Int. Med. 15: 1059 (June) 1915.

11 Barach, J. H. Blood Pressure Studies in Typhoid Fever, Penn M. J., March 19, 1907.

The slow pulse accompanying hypotension in influenza is noteworthy. Hypotension occurs in about 35 per cent of normal soldiers, but it occurs in 100 per cent of soldiers with influenza.

Acute "Colds"—In acute infections of the upper respiratory tract, such as rhinitis and bronchitis, when the patient complains of muscle pains, chilliness, cold hands, cold feet and shivering, with a normal or subnormal temperature, if such a patient's blood pressure is taken, one will find a temporary hypotension.

Pneumonia—In pneumonia, there is practically always a marked fall in the blood pressure, so much so that a well known rule has been formulated by Gibson to the effect that a bad prognosis is indicated if the pulse rate is higher than the figures for systolic pressure. Experience has shown that this rule is not a reliable guide, it has, nevertheless, called attention to an important phase of the disease.

It is interesting to note that in acute infectious diseases involving the respiratory tract, arterial hypotension is most marked. Even in typhoid fever, the respiratory tract is not a negligible factor. In 500 cases of typhoid fever,¹² I found symptoms and physical signs of bronchitis in 20 per cent and pneumonia in 5 per cent. Those of us who have treated many typhoid patients have known the frequency of hypostatic congestion of the lungs.

In these acute infectious diseases there is a tendency to cyanosis most marked in influenza, constant in pneumonia and present also in typhoid fever. In typhoid fever, it is noticeable in the dusky, fevered face, and in the bluish color under the nails. In these diseases, cyanosis and increased respiratory rate indicate the degree of respiratory deficit.

There are other acute infections, among them erysipelas and diphtheria, in which hypotension occurs and in which the mechanism is probably the same. Oxygen requirement is high in all fevers, irrespective of the type. We should keep in mind that oxygen want may be produced by a high rate of expenditure, a lower than normal oxygen intake, or both, and that oxygen deficit is the result of diminished vital capacity, a diminution of the respiratory surface, and impermeability of a diseased respiratory mucous membrane. One thing stands out clearly, and that is, that in acute infections in which hypotension occurs, we find evidences of a respiratory deficit and, therefore, of oxygen want.

HYPOTENSION IN CHRONIC DISEASES

Pulmonary tuberculosis is accompanied by a very marked degree of arterial hypotension. All observers are agreed that hypotension is

¹² Barach, J. H. Clinical Observation in Five Hundred Cases of Typhoid Fever, International Clinics 11, Series 19, 1909.

a characteristic of the disease. The degree of hypotension is proportionate to the extent and severity of the disease. In this disease, respiratory deficit and arterial hypotension go hand in hand.

That anemias are accompanied by hypotension is well known. In Addison's disease, hypotension is said to be most marked. After cardiac decompensation has begun, blood pressure falls.

Diabetes is a disease in which we find both hypotension and hypertension. Hypertension in the type associated with sclerotic vessels and nephritis, hypotension occurs in those cases in which there has been great loss of flesh and strength, and in which there is an accompanying weakness. My records in the last eighteen months show that, in 118 cases of diabetes, forty-four had a systolic pressure of 110 mm. of mercury, forty-six had a systolic pressure of from 110 to 150 mm., and twenty-eight had a pressure higher than 150.

Hypothyroidism and those inseparable endocrine disturbances corresponding closely to the clinical picture of hypothyroidism constitute a group in this series. All patients in this group had a minus basal metabolism and showed a great tendency to hypotension, irrespective of their obesity. These patients suffer decreased oxidation, which, of course, is different from oxygen want, although the effect on arterial tension may be the same.

Of twenty-three such patients, twenty had marked hypotension. Their average basal metabolic rate was minus 10 per cent, but two thirds of them had a basal metabolism of minus 15 per cent or more. For the series, the average systolic pressure was 99 mm. of mercury, and the diastolic was 66. The average weight for the group was 35 pounds (15.9 kg.) above normal standard.

In chronic respiratory diseases, such as tuberculosis, the patient's respiratory deficit comes from the consolidated lung and muscular weakness, both reducing pulmonary ventilation. In anemia, the oxygen carrying power of the blood is deficient. In hypothyroidism, the oxygen consumption is diminished.

ESSENTIAL VASCULAR HYPOTENSION

Let us now consider a group of 100 cases in which arterial hypotension constitutes the most marked abnormality in the individual. This type has been called essential hypotension. (The group does not include recognizable cases of severe anemia, cachexia, pulmonary tuberculosis, Addison's disease, hypothyroidism or any recognized cardiovascular diseases.)

There were, in the entire group, forty males and sixty females. Without going into a detailed analysis of symptoms, which would be endless and without profit, and without classifying the various diag-

noses that were made in these patients, and which, if proved, would probably be wrong in about one-half the cases, I am going to offer my general impression of their most marked characteristic.

Taken as a group, the subjects are distinctly undersized. They are nonathletic. They have narrow nostrils and, frequently, nasal obstructions; they have narrow chests and slender bodies. They distinctly belong to the hyposthenic and asthenic type. They have a smaller than normal chest capacity, and they have a marked tendency to muscular relaxation. Frequently, they have drooping shoulders, and they are shallow breathers. At times, we note irregular breathing. This irregular breathing is similar to the periodic type of breathing seen in newcomers to a high altitude, which is plainly due to oxygen want and is promptly relieved by oxygen inhalation.

ARTERIAL HYPOTENSION AFTER MIDDLE LIFE

In a group of forty-six patients, ranging from 60 to 90 years of age, I find that there were five whose systolic blood pressure did not exceed 110 mm of mercury. I know that some of these had arterial hypotension for many years, and I have seen the blood pressure recede from year to year, with the advancing atrophy of muscle and subcutaneous tissues. In some individuals of this type, I believe that the oxidative process, throughout their long lives, runs on an economic basis, which would, in part, account for their longevity. It is interesting to recall that Fisher of the Northwestern Mutual Life Insurance Company found that, after middle life, hypotension patients live longer than persons whose pressure does not exceed 148 mm of mercury.

SUMMARY AND CONCLUSION

The incidence of arterial hypotension is fairly constant, and it is found in about 35 per cent of persons in apparent good health. As previously pointed out by others, the individual who has hypotension is physically subnormal and is of the hyposthenic or asthenic type. My strong impression is that he has been endowed with a poor respiratory apparatus.

A normal person subjected to a diminished oxygen supply, such as occurs at high altitudes, will have a lowering of blood pressure. If he is of the sthenic type, he adjusts himself well, if he has a poor respiratory apparatus, he is sure to experience a more or less severe attack of mountain sickness. All this can be produced artificially, in a closed chamber, by reducing the oxygen supply.

In the acute infectious diseases, especially those involving the respiratory tract, in which a respiratory deficit occurs, hypotension is found. In chronic pulmonary diseases and in certain metabolic disturbances in

which there is a subnormal oxidation, and in other diseases in which there is an insufficient volume of blood to carry oxygen, as in hemorrhage or pernicious anemia, or in which the blood is a poor oxygen carrier, we again find arterial hypotension. All the evidence, when correlated, seems to point significantly to the deduction that when there is a respiratory deficit and decreased oxidation, then we find arterial hypotension. It is an easy step forward, if one is willing to take that step, to assume that we are here dealing with a cause and its effect. If this holds good in the light of further experience and observations, then, in stating the causative factors of arterial pressure, we will write that arterial pressure is dependent on energy of the heart, the resistance in the arteries, and the quantity and character of the blood. But we will place before these and as the first factor "respiratory effort and oxygenation."

A QUANTITATIVE TEST OF DIGESTIVE PANCREATIC ACTIVITY, EASILY APPLIED CLINICALLY

TESTS FOR VOLUME OF PANCREATIC JUICE AND BILE SECRETIONS¹

ANTHONY BASSLER, M.D.

NEW YORK

The value of some clinical method of estimating the digestive activity of pancreatic juice is apparent. Extraction of small portions of the duodenal contents and the testing of the return to note the presence of enzymes have been devised, but all of the methods are only qualitative, and the admixture action of the enzymes takes place outside the body instead of *in vivo*. For these reasons, they have not been popular. A method that called for the use of tubes filled with various substances had been suggested,² in which the element of error is too great for clinical purposes. Another method, much more accurate but quite impossible as a routine clinical procedure, has been devised³ in which the three enzymes are estimated. The oil regurgitation method of Boldyreff and Volhard is not practical. The best work thus far reported has been done by Crohn,³ and acknowledgment is made of its assistance. A method of examination is herewith described in which the secretion and admixture of pancreatic juice takes place normally and within the body, which is sufficiently accurate for clinical application, is easily and quickly carried out, and does not require much special apparatus, solutions or technical knowledge for its performance. In its application, thus far, it answers fair better in noting deficient pancreatic function than the examination of feces, because shades of difference in activity are not possible of being deducted from stool examinations. In these, when the examination shows many and striated muscle fibers, steatorrhea and fatty acid crystals, the pancreas is generally markedly advanced in dysfunction. Other conditions than pancreatic disease may give positive findings, and often, in distinct pancreatic involvement, the feces tests are normal owing to enzyme activity of intestinal bacteria supplanting deficient pancreatic secretion.

¹ Read before the Section on Gastro-Enterology and Proctology at the Seventy-Fifth Annual Session of the American Medical Association, Chicago, June, 1924.

² Einhorn, Max. Agar Tubes for the Estimation of Pancreatic Ferments, M. Rec., Oct. 12, 1912.

³ McClure, C. W., Wetmore, A. S., and Reynolds, Lawrence. New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man, Arch. Int. Med. 27:706 (June) 1921.

³ Crohn, B. B. Am. J. M. Sc. 114:393 (March) 1913, Arch. Int. Med. 15:581 (April) 1915.

In the development of the method suggested, much work has been done against the many difficulties that are encountered in digestion in the duodenum and laboratory procedures. There are said to be four enzymes in pancreatic juice: lipase, amylase, trypsin and rennin, the first three being important. Since rennin (the existence of which I question) is also present in the stomach (which I also question) it was not considered. The original work was done on trypsin. With pepsin in the gastric juice and the jets through the pylorus carrying this ferment and even the end products of peptones, no sharp deductions of trypsin activity could be gained, this being further confused by the unknown factor of enterokinase from the duodenal mucosa, the activator of trypsin. It was learned here, however, that in achylic stomachs, free from pepsin, that the factor of pancreatic trypic activity was capable of converting ample amounts of native proteins for nutritive balance. Because of the occurrence of lipase solely in the pancreas, its quick ability to attack neutral fat, the steadiness with which this activity was met with, its quick secretion and in frank amounts, two years time was employed in studying and utilizing this ferment as the basis of the test. As experience multiplied, two factors persisted in bringing so much discouragement about that it was abandoned, these being the bile factor and the reversibility action of this enzyme. This left amylase, which serves as the basis of the test, and enough work has been done on it to prove it to be practical. After the thirty-second procedure of methods and tests, the following plan was found to be the most practical and is accurate within a small amount of error (not more than 5 per cent). It may form part of a bile aspiration conducted for diagnostic or therapeutic purposes.⁴

On an empty stomach, preferably in the morning, the tip of a duodenal tube is passed into the duodenum until, by fluoroscope, it is noted that the tip is at least 10 cm., or 4 inches, beyond the pylorus, water being used to assist in accomplishing this. For this, to meet the variations in all individuals, a longer tube length than that of most duodenal tubes

4 As the peptone solution is ordinarily made, it contains an amorphous debris, and this would be confusion in an A or B fraction examined for diagnostic purposes, as Lyon suggests to be done with magnesium sulphate solution. In such an instance, I advise that the peptone solution be used instead of the magnesium sulphate, but that the peptone solution be filtered through absorbent cotton. Lots of 100 cc each can easily be made up, and, if sterilized, will keep well until used. The magnesium sulphate solution will give pancreatic results, but it is too variable to depend on, the food shock of peptone being a far better pancreatic stimulant. If a peptone solution is used first and, for any reason, later followed by a solution of magnesium sulphate, nausea is very liable to follow. Therefore, when starting with the peptone solution, one or several doses answer satisfactorily for the accomplishment of a complete "medical gallbladder aspiration" without using magnesium sulphate at all. Usually only one dose is sufficient for a full functional return.

is essential (tube length 125 meters, or 49 inches) The patient is then given an injection, through the tube, of 100 cc of a 5 per cent Witte peptone solution, and five minutes is allowed for it to pass beyond the duodenum, at which time the duodenal return is aspirated by a suction bulb through a 200 or 250 cc intervening bottle In a few moments, the so-called "*A* fraction" begins to flow and aspiration is continued until about 20 cc is collected, or until the *B* fraction starts The *A* fraction is employed in the test because this consists mostly of pancreatic juice and only a small amount of bile admixture The *B* fraction is from the general bile passages (not necessarily only from the gallbladder) and contains less pancreatic juice than the *A*, but more bile The *C* fraction is from the smaller bile radicals in the liver, and contains decidedly less pancreatic juice than even the *B* The *A* fraction represents the sudden secretion of the stored-up activity of the pancreas The more normal the gland, the greater the storage, and vice versa The storage factor and promptitude of flow are the two factors that the test depends on for normal readings in addition to the enzyme quality of the juice secreted Since the enzymatic action of this early return from the duodenum may change quickly, it should be tested at once It will be found that the *A* fraction obtained in this way is strongly acid in reaction Amylase works well in both acid and alkaline mediums, but there is a slight difference in the rate depending on the intensities For the purpose of standardizing the test and raising the p_H value to about 70, the *A* fraction (or about 15 cc of it) should be rendered slightly alkaline with saturated solution of sodium carbonate until it just shows faint pink on mixture with a weak phenolsulphonphthalein solution, although in routine work this is not necessary No dilution of the duodenal return is made for the test, the return being taken just as obtained plus the few drops of alkaline solution, or without

The method employed to test the amylase content is a modification of that advanced by Smith⁵ for ptyalin, and rendered applicable to conditions met with in amylase and the admixed duodenal return The degree of enzyme activity measured is the quantity that will just cause a disappearance of iodin color producing substance, under conditions described, in 20 mg of corn starch (Duryea) contained in 5 cc solution with a stabilized hydrogen-ion concentration corresponding to p_H 67 or the use of plain water, which has a p_H value of 70 and which is normal for duodenal enzyme activity, and with electrolytes furnished by the presence of 0.05 sodium chlorid The quantity of return from the duodenum in the *A* fraction that produces this result is arbitrarily

5 Ferris, H C, Smith, E E, and Graves, E V J Am Dent A, January, 1923

regarded as containing one-fiftieth unit of amylase, the unit being the quantity of amylase that will digest 1 gm of starch under conditions outlined

TECHNIC OF TEST

The reagents are 1 A standard starch p_H 6.7 sodium chlorid solution made up as follows

To solution *a*, when cool, 50 c c of solution *b* (as mentioned above, plain water acts quite as well), and 25 c c of solution *c* and distilled water should be added to bring the volume of the mixture to exactly 400 c c This should be freshly prepared

Solution *a* is corn starch solution In a beaker, 2 gm of the starch to 100 c c of cold distilled water should be mixed thoroughly and then heated Under constant stirring, this should be brought to boiling and then cooled

Solution *b* is a standard buffer solution p_H 6.7 prepared as described by Clarke,⁶ 50 c c fifth molar acid potassium phosphate and 21 c c fifth molar sodium hydroxid solution are accurately delivered in a 200 c c volumetric flask, and the contents brought to the exact volume with distilled water⁷

Solution *c* is a 1 per cent sodium chlorid solution

2 A twenty-fifth normal iodin solution, with a dropper cork in the bottle

The reagent solution should be ready so that no time is lost in carrying out the test, because pancreatic solution is stated to lose its diastatic efficiency at room temperature at the rate of about 25 per cent in the first twenty minutes after extraction, and 70 per cent in three hours⁸

The procedure is as follows

In each of ten tubes (6 by 0.5 inches [15.2 by 12 cm]) in a rack and numbered from 10 to 1, one should accurately pipet with a 1 c c pipet marked in hundredths, fraction *A* of the duodenal return, water and reagent as shown in the accompanying table

⁶ Clark, W M Determination of Hydrogen Ions, Baltimore, Williams & Wilkins Company, 1920, p 70

⁷ The p_H of the most active pancreatic digestion is about 7.0, the p_H value of water Thus, in the absence of the buffer solution, plain water may be employed, the result being practically the same

⁸ This rapid rate of loss of activity has not been confirmed in my observations, at least not with the returns from the duodenum In many observations, the loss up to as long as six hours was negligible in returns from the duodenum, whereas with alcoholic water extracts of the pancreas it is rather rapid Therefore, the aspirated return in the test may be examined some hours afterward even though it remain cold in the interval

Procedure of Test

Number of tube	10	9	8	7	6	5	4	3	2	1
Duodenal return, c c	0.1	0.11	0.125	0.14	0.17	0.20	0.25	0.33	0.5	1.0
Water, c c	0.9	0.89	0.875	0.86	0.83	0.80	0.75	0.67	0.5	0.0
Reagent, c c	4	4	4	4	4	4	4	4	4	4
Units (author's) per 100 c c	20	18	16	14	12	10	8	6	4	2

When set up, shaken and ready, the rack is put in an incubator at 38 C or a water bath for thirty minutes. The rack of tubes is then taken out, the contents of each tube is shaken, a drop of the twenty-fifth normal solution of iodin is added to each tube beginning with Tube 1, twenty minutes time is allowed for the changing of colors to become settled, and the estimation of units is made according to the furthest tube to the left that is achromic. The result is then expressed in units of pancreatic enzyme efficiency. No more than the one drop of iodin solution should be added because the more the iodin, the deeper the colors, the less definite the comparison and the less accurate the test.

Ordinarily, the tubes having the largest amounts of duodenal return will be green. This shades down from Tube 1, becoming lighter and fainter to one having a colorless content. The achromic tube represents the amount of return from the duodenum that contains one-fiftieth unit of amylase. Generally the tube to the left of this tube shows a light pink or gray and those more toward Tube 10 shade deeper into reddish purple. At the achromic zone, should the right tube be a sage green and the one to the left of it a very light pink, the achromic point would be between these two tubes. For instance, if Tube 5 were green and Tube 6 pink, the units per hundred cubic centimeters would be 11. The tube that contains the one-fiftieth unit is divided by 50, which gives the units per cubic centimeter. The calculation used is:

Units of amylase in 1 c c duodenal return = units amylase (pancreatic efficiency) per hundred cubic centimeters duodenal return

For instance, in a test that shows achromic in the sixth tube

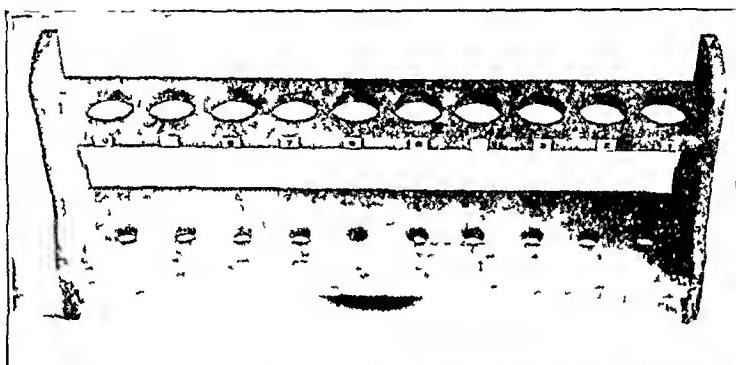
$$\begin{array}{r} 1 \ 2 \\ 50 \overline{) 6 \ 0 \ 0} \\ \underline{-} \ 5 \ 0 \\ \underline{\quad\quad\quad} \\ 1 \ 0 \ 0 \\ \underline{-} \ 1 \ 0 \ 0 \end{array}$$

$$0.12 \times 100 = \text{pancreatic efficiency of } 12 \text{ units (author's)}$$

It will be noted that the test is so arranged that the result in units is double the number of the tube in which the reaction occurs, thus the sixth tube equals 12 of my units.

The test, as described, takes care of most instances of low pancreatic activity, and meets clinical requirements in a routine way. Should no achromic point be present in the first tube, a greater amount of duodenal return may be used, and, according to the amount employed to arrive at the achromic point, a calculation may be made.

The test is so arranged that the extreme normal ranges occur between the fourth and the seventh tubes (from 8 to 14 units), giving sufficient tubes for errors of the gland on each side of these. The average units in normal persons are between 10 and 12, and, as experience multiplies, we find 6 units is suspiciously low (slight hypopancreorhea). Up to the present, in even late carcinoma, marked fibrosis, or acute and suppurative pancreatitis, the test, as outlined, answered for the low unit readings. In very active secretion, the dilution may be increased and calculated accordingly. The various contents should be added to the tubes, beginning with Tube 10 on the left and working to Tube 1 on the right. This rule should be carried out to the end of the test. This preserves the proper intervals of time in the various additions. Usually, not more than ten minutes are necessary to prepare the tubes in the rack, and this need not be figured off the incubator time (thirty minutes).



Wooden test tube rack with numbers of tubes, and, below, the amounts of duodenal return, reagent and water, written so they can readily be followed. The rack is the usual form found in any laboratory, and the numbers can easily be attached.

Every method to estimate the enzymatic action of the duodenal contents must combine delicacy, uniformity, proportion of enzyme activity and accuracy of estimation. Unless a method adheres to these, it is of little value clinically. Also, it must be possible of quick performance or it would not be used as a routine in examination. The method advanced is quantitatively accurate and meets every clinical requirement. No test that does not take into consideration the change in hydrogen-ion concentration incident to the action of an enzyme being met by buffer solution serves to much value (plain water controls this accurately enough). This is as important a factor as the temperature in which the enzyme works,⁹ and this is one of the main reasons why former methods have been of so little value.

There are, no doubt, chemical and physical factors of variation in different persons, and in the same person at different times, which give different results, but, in my experience, these are not much beyond the range of the normal set for the test. Up to the present, depressing emotional factors, which can so readily affect the salivary and stomach secretions, do not seem able so definitely to depress the pancreatic and hepatic secretions, although, in a few instances, this has occurred. The pancreas and biliary apparatus in the liver are more dependent on food stimulation, and it is for this reason that any test that does not combine a food stimulant is of little value in clinical work. Thus, the testing of a return from the duodenum in which a food stimulant has not been used is of little clinical value. The peptone solution is a quick and abundant stimulant of the pancreas even when brought in contact with the mucosa well on in the third part of the duodenum. By employing the food stimulant, we obtain the storage factor of the gland, and, as a pancreas is deficient in this, it is deficient in its running secretory function. The storage factor of all gland cells during rest is the best index of the organ function and of its activity during the complete range of active secretion.

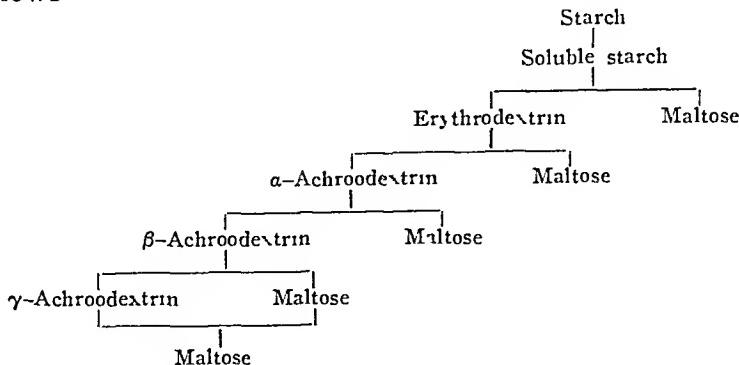
Argument may be presented that a test for amylase enzyme alone is valueless in judging the other enzymes and, in that way, the total function of the pancreas in digestive juice. Perhaps this would be true in very exceptional instances which up to the present time have not been met with in hundreds of estimations in normal and diseased pancreases. Checking the proteolytic and lipolytic activities of duodenal return against the amylolytic, with the best means on hand, shows that, within small percentages of difference, they all run together. When one is low, the other two are correspondingly diminished, and when the pancreas is functioning so that one is high, the other two also are high. This is against the assumed belief, but it is clinically true. There are two types of cells in the salivary glands and two types of cells in the gastric tubules, yet there is only one enzyme secreted by each of these organs. The pancreas, other than the spindle-shaped cells of Langerhans, which probably are concerned in internal secretion, contains only one kind of two zoned acinous cell, and it is reasonable to assume that the three enzymes or proenzymes come from this cell. It therefore follows in reason that when this cell is deficient in enzymatic power, this deficiency would be represented in all the enzymes instead of in one and not in another. Argument may be presented that an enzyme content is dependent on demands of a diet. This is true when a definite character of diet has been kept up for lengths of time, but the patients examined at the time have been on mixed meals, so this argument does not hold, and

even for people who have been on a high fat, carbohydrate or protein diet, the other enzymes than those called in demand still have been found proportional in the many tests that have been made.

Enzymes are catalysts, that is substances capable of initiating a reaction without entering into it integrally. They are unorganized substances, usually hydrolytic in character. As a rule, they are specific. The products of the pancreatic amylase (amylopsin) on starch are the dextrans, with maltose and glucose as the end products. Because of the impossibility of preparing an enzyme and their great liability to change, their action can best be studied by *in vivo* methods. Each enzyme shows its greatest activity at a certain temperature, the best known having an optimal temperature between 35 and 45°C and usually requiring a medium in reaction suitable for the enzyme. In respect to many enzymes, as with inorganic catalysts, the intensity is almost directly proportional to the concentration of the enzyme, and the relative concentrations are directly proportional to the squares of the intensities, this is true with amylase, and has been provided for in the test. An anticatalyzer exists for amylase as for other enzymes, this being a factor in the test not possible of estimation, at this time. However, it does not seem in any way to influence the test, probably because the function of an anticatalyzer is only protective to the mucosa of the intestine from autodigestion, as the anti-enzyme (antipepsin) in the stomach protects the stomach from digesting itself, and is not active outside the body. From my studies, I believe it is possible that saliva as a digestive fluid is not absolutely essential nor a factor to consider in the test. Its action is stopped by the hydrochloric acid of the stomach, and ptyalin is not active in the duodenum. At any rate, no saliva is introduced into the duodenum, so this does not concern us in the test. The pancreatic amylase (amylopsin) is much more active than ptyalin but slower to start, is secreted in larger quantity and is active under alkaline, acid and neutral reactions. Pancreatic amylase will digest the raw starch of corn and wheat completely but potato starch only to about 80 per cent, therefore, corn starch is used in the test. At the proper temperature and alkaline reaction conditions, marked starch conversion takes place in an hour or two. Chilling of the test tubes with ice water promptly checks amylase activity, but its activity can be restored at 40°C, for this reason, it is often wise to chill the tubes before the twenty minutes standing.

Accompanying each dextrin, a small amount of maltose and glucose are formed, the quantity of maltose growing gradually larger as the process of transformation progresses. As each new dextrin is formed from soluble starch, a portion of maltose is formed by hydrolysis—thus,

the sugar content is difficult of estimation Hawk graphically illustrates this as follows



In addition to the foregoing, it is proved that with pancreatic amylase the amyloclastic tests correspond to the saccharogenic,¹⁰ and, since they are simpler to perform and with less error in estimation of the amounts, they are to be desired in this work

The amylase of the pancreas converts starch into dextrin more rapidly than the dextrin into maltose Amylopsin, however, is capable of dissolving and digesting very large amounts of starch Bile and duodenal juice do not affect the amylolytic action of pancreatic amylase, and if they do, in nonappreciable amounts It has been reported that tests made with certain extracts of the pancreas are sometimes found which convert starch to dextrin with great speed, but which have little or no saccharifying power For this reason, some observers seem convinced that there are at least two different enzymes in amylopsin, one an amylase which converts starch into dextrin, and one or more dextrinases which convert dextrin into maltose It has been stated that these two enzymes are associated, but it may happen that they exist separately, or the dextrinase may be destroyed, wholly or partly, leaving the other active As far as my observations have gone in returns from the duodenum, this is not true and need not concern us In the test, only the first conversion of starch is estimated With the smallest amounts of amylopsin secreted in a normal way from the pancreas, starch conversion to sugar is in steady relationship to amounts of enzyme and starch In the enzyme digestion of the starch solution, the opalescence first disappears forming a soluble starch which gives a blue color with iodin, then erythrodextrin, which gives red with iodin, then the achroodextrins which give no color with iodin A yellow denotes complete starch digestion in concentrated mixtures Practically, starch contains ten chemical compounds of sugar, but, in the hydrolyzation this figure does not maintain in percentages of sugar production at any

¹⁰ Sherman, H. C., and Schlesinger, M. D. J. Am. Chem. Soc. **37** 1318 (May) 1915

conversion period. The whole course of pancreatic starch conversion is in steady increasing percentages of sugar, glucose as well as maltose.

In the work with the various food elements and different tests, it has been proved that when the duodenum and the stomach are empty there is no secretion of pancreatic juice, or it is practically nil, and the flow of pancreatic juice keeps up only as long as food is coming through the pylorus or food is thrown into the duodenum. It is true that after a mixed meal, from two to four hours represents the maximum quantity of pancreatic juice (this being the time in which the greatest amount leaves the stomach), but the juice at this time, in a unit, is not as rich in enzyme content as the initial flow, thus, this storage factor is taken advantage of as the standard of enzyme content of the juice and gland ability, rather than the later phase of secretion.

The amylase found in the feces is no doubt derived from pancreatic juice, but whether that in the blood and in the urine also is derived from it is not positively known, although there is much reason to suppose that it is. In regard to the blood and the general body tissues, there is reason to assume that it gets into the general body from resorption into the portal blood. There is now considerable evidence to believe that this systemic content of amylase has something to do with general body nutrition, although it is impossible at present to state when sub-nutrition of body structure exists and the blood, stool and urine contents of amylase are low (and this also is proved in the test from the pancreas), how much is effect and how much is cause. Banting and Best have drawn attention to the importance of Langerhans' islands in the systemic combustion of sugar. There no doubt are systemic effects due to deficiency of gland function other than that produced by products of the connected islands of Langerhans. These are probably nutritional, and have been brought about by deficiency of carbohydrate conversion, resorption or hepatic cell storage ability. Apart from these are the errors of digestion due to abnormalities of function in producing clinical symptoms in the alimentary tract. Much work has still to be done, but as far as we have gone the future will warrant the use of such terms as hypopancreorrhea, hyperpancreorrhea, hypocholia and hypercholia.¹¹

The theory of Solinsky, that acidity of gastric juice brought in contact with the mucous membrane of the duodenum sets up promptly a secretion of pancreatic juice, and the deduction from this that the

¹¹ One might as well be philologically accurate when coining new terms in medicine. The new terms hypopancreorrhea and hyperpancreorrhea employed in this article are more expressive than hypopanchrea and hyperpanchrea although the latter are correct. The terms hypobilia and hyperbilis are hybrid (hyper is Greek, bilia is Latin) thus correct Greek would be expressed in the terms hypocholia and hypercholia, and these terms are recommended for use.

acidity of the gastric juice is the means that serves to inaugurate the flow from the pancreas, have not been proved in my observations in studies on lipase. This also holds good against Bayliss and Starling's belief that secretion is initiated by gastric acidity. Food substances, such as peptone and neutral oils and the starches delivered into the duodenum, do cause a prompt and vigorous pancreatic flow without acid.

The results in the test are sharp and somewhat like test meal extractions of gastric juice and more important clinically. The application of this method of examination opens up a field of interest in the most important of all digestive organs (the pancreas), which heretofore has not received much attention because of the impossibility of direct approach in examination, because proper stimulation was not employed, on account of the absence of a dependable clinical test, and because approximate *in vivo* methods were not employed. The test has proved that the digestive ability of the individual and the general state of nutrition largely depends on the quality of pancreatic juice or the enzyme content of the duodenum. Hypopancreorrhea is a clinical entity of no small moment. After critical analysis and considerable experience, I feel that the test deserves to become a routine of examination, and, further, that by its employment we are entering into a field of clinical development that will add distinctly to gastro-intestinal work.

ADMIXTURE FACTOR TO FOODS

It sometimes is desirable to learn what the admixture factor to foods is in the duodenum as a part of the test. A pancreatic juice may contain a greater or lesser amount of enzyme index than normal, it may be hyperfluid or diminished, and stenosis of the duct or at the ampulla may exist. In the test outlined in the above, a juice may very occasionally show a low enzyme index in a unit of return, because the return is watery compared to normal, or it may be too high because of concentration. In abnormal findings of the test described, it is well at times to find out what the admixture factor is, and, while the procedure about to be described has an element of error, it is still accurate enough for clinical purposes. For this test, when the tip of the tube is in the duodenum, the patient drinks the following mixture through a glass tube and lies on the right side. Two hundred cubic centimeters of a 5 per cent starch solution is made up in the usual way, when cooling, 18 gm of sublimed sulphur is mixed with it in a shake flask (Erlenmeyer), some large faceted beads being used to help in making the mixture uniform. This mixture will hold the sulphur in uniform suspension up to the end of the test. Having quite a flat taste, the mixture may be flavored with a few grains of saccharin and vanillin crystals.

Two Hopkins vaccine tubes are used in the test. Tube A contains part of the original starch mixture and is used as a control. Tube B contains the return from the duodenum. Each tube is filled accurately to the 5 cc mark and centrifugated for about two minutes at high speed. A wire with a slightly bobbed end is run down through the sulphur crystals to rearrange them, and free any bubbles or clots of starch that may have gotten in the small end. They are then centrifugated again for a minute or two, the crystals rearranged as before, and, finally, centrifugated for two minutes more. The difference between the sulphur level in the two tubes gives the admixture percentage.

Example Tube A, 51 spaces, Tube B, 25 spaces

$$\begin{array}{r}
 & & 4 & 9 \\
 & 5 & 1 & | & 2 & 5 & 0 & 0 \\
 & & 2 & 0 & 4 \\
 \hline
 & & 4 & 6 & 0 \\
 & & 4 & 5 & 9
 \end{array}$$

$$100\% - 49\% = 51\% \text{ admixture of duodenal contents}$$

It must be remembered here that water and starch do not stimulate bile flow, and such flow that may be in a return is trivial. Often, when conducting this test and bile is flowing into the duodenum, as promptly as the starch solution is given by mouth, it is checked. It is better to conduct the admixture test on a subsequent day to the one for enzyme. Obviously, with an enzyme result, and a higher or lower than normal admixture result, the unit reading of enzymatic power would have to be expressed in terms of admixture, almost all of which is pancreatic juice. The range of normal for admixture is from 40 to 80 per cent, with an average normal of 58 per cent in several hundred instances. The lengths of time for the starch to appear in the bottle is from five to fourteen minutes, with an average of six minutes, and the time for sufficient return for the tubes runs from three to twenty-five minutes, with an average of fourteen minutes. This test may be employed to diagnose stasis or obstruction in the duct of Wirsung or at the ampulla (diminished quantity of pancreatic juice with normal enzyme activity). This test is only approximately accurate.

STASIS AND OBSTRUCTION

It may be desirable at times to have some means to diagnose stasis and obstruction (partial as well as complete) in the biliary ducts. The method employed answers in this to clinical advantage. Usually this can be assumed in the ordinary medical bile aspiration when magnesium sulphate or peptone solutions are used as stimulants. A prompt bile admixture and a quick appearance of the *B* fraction denotes patent ducts. It serves the purpose at times to estimate this in a definite way, and the

method employed has been satisfactory for use. Fat is an intense stimulant to bile flow, bile being necessary for fat digestion. The patient is prepared as in the foregoing tests with the tip of the tube in the duodenum. Then about 100 cc of olive oil is drunk, and the patient lies on the right side. In a few minutes, a return is obtained, and 10 cc of this is centrifugated in a graduated centrifuge tube. The percentage of duodenal secretion in this test, almost all of which is bile, in the extreme ranges met with were 59 to 99 per cent, 84 per cent being the average. The lower the percentage of admixture the surer we may be of the existence of stasis or obstruction in the bile passages. The bile and oil return appears from two to twenty-five minutes (average nine minutes), and a sufficient amount for the test in from seven to thirty minutes (average fourteen minutes).

The difference between the admixture result in the starch test for pancreatic juice and the oil test for bile represents bile flow, which in the normal is approximately 35 per cent higher in the second, this 35 per cent runs true in the low admixtures as well as in the high. Anything below 35 per cent means either excess pancreatic secretion, too low bile secretion, or delivery (biliary stasis). This test is only approximately accurate.

METHODS OF STUDYING FAT DIGESTION

My associate, Dr Lutz, and myself¹² have suggested methods of studying fat digestion in the human being under the microscope. If the duodenal tube is left in the duodenum some minutes longer (from ten to fifteen), the return then examined under the microscope will demonstrate these and give a fair idea of lipase activity existent in the individual, although not sufficiently accurate for clinical conclusion. One must be careful here to neutralize the return if it is acid, or the changes will not be observed.

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ABSTRACT OF DISCUSSION

DR BURRILL B CROHN, New York. This is an era of great interest as regards functional activity and functional tests. Any addition to our knowledge on this subject, particularly in connection with so obscure an organ as the pancreas, is welcomed as an asset of great value. The interest in pancreatic function really goes back to the time when Dr Einhorn first introduced the duodenal tube in this country. Previous to that event, pancreatic functional tests depended on stool examinations which were more or less inaccurate, probably more inaccurate rather than accurate. Stool examinations, as done ten years ago, were very inaccurate. It is of interest that Dr Brown of Baltimore utilized to his own satisfaction the amylase test both in the stool

12 Bassler, A., and Lutz, J. R. Demonstration of Human Digestion of Fat Under the Microscope, Am J M Sc, December, 1924.

and in aspirated fluids from the duodenum for the purpose of studying the pancreatic ferments. In former years, it was quite common to criticize any of the pancreatic quantitative tests, on the basis that no quantitative test of pancreatic enzymes could be accurately carried out. It was pointed out that the presence of a considerable amount of saliva, gastric juice and biliary secretion so diluted the duodenal contents that no quantitative study of the pancreatic ferments would hold. In spite of the theoretical objection that the presence of four or five different fluids in the duodenum makes it difficult to get an accurate test, those who have worked on pancreatic tests through aspiration from the duodenum have convinced themselves that this method does give valuable information. In spite of the fact that the pancreas itself furnishes a tremendous factor of safety, in spite of the fact that nine tenths of the pancreas can be destroyed without there being any physiologic evidence of pancreatic insufficiency, quantitative tests of the ferments in the duodenum are satisfactory as an index of pancreatic functional activity. I should like to endorse what the author has said about the simplicity of the methods necessary. The simpler test, such as the casein test for trypsin, the very simple Wolgemuth test of soluble starch and iodin, is very easily carried out and give accurate data. I myself found the trypsin test more accurate than the amylase test. The former I have found to be reliable and very satisfactory.

DR DANIEL N SILVERMAN, New Orleans. Heretofore, the estimation of the amylase has been performed by the estimation of the end products of digestion, that is, the amount of sugar converted from the starch. But Dr Bassler's method is an advance, in that he measures not the amount of end products, but the amount of duodenal product that is required to digest a definite quantity of mixture. This represents, as we know, only a part of the external pancreatic function as tested in various ways. I must say something in defense of the McClure method, which I have used ever since McClure advanced it, about three years ago. Dr Denis of Tulane University of Louisiana School of Medicine and I have performed great numbers of tests on both normal and pathologic subjects. In our examination, we have followed the method of McClure in estimating three of the enzymes, and I must say that we have not been able to come to the same conclusion as that arrived at by Dr Bassler, that the standard or the strength of the amylase will correspond to the strength of the other two enzymes, protease and lipase. Of course, the estimation of all these enzymes represents the external function of the pancreas. It has been our experience that the external function of the pancreas may be greatly inhibited and yet there be no disease whatsoever. In the severest case, it was our observation through histologic study to find that the pancreas was not involved and that the secondary disturbance was due to carcinoma of the liver and gallbladder. In accord with McClure, it is our observation that cream acts as an excellent stimulant to pancreatic secretion. We have examined fluoroscopically each and every one of our tubes in order to visualize definitely the position of the tube in the second portion of the duodenum. In the study of the duodenal contents for its pancreatic activity, the reaction of the duodenal contents has a great deal to do with the results. We find, in perfectly normal persons who are fasting, that if the duodenal contents are acid the enzymes are somewhat inhibited and sometimes absent. We have been able to check up our results of examinations through use of the duodenal tube, by means of a fistula in man. We found that the reaction of the duodenal contents through this fistula also at times became acid.

DR ANTHONY BASSLER, New York. Except to say that there is no dissociation between the enzymes, I desire to repeat that we checked up all our work with the McClure method, and the McClure method, so far as the estimation of trypsin and lipase is concerned, is valuable. I have no criticism of it, but it is as complicated and difficult to perform as a blood chemistry

examination, and that makes its use impracticable. I am now of the opinion that what we have called lipase as an enzyme, in all probability, does not exist. One can accomplish every phenomenon which I have shown you on the screen without lipase, and simply the sodium carbonate that is in the normal pancreatic secretion can produce the reduction of neutral fats. There is considerable doubt in our minds now that lipase is a ferment. In surgical work, in the study of function in connection with intestinal digestion, in metabolic or nutritional estimations, and even in diabetes, we commonly get these hypopancreatic results, and I believe that we have gone sufficiently far now with the test in cases so that we can predict a lesion in the pancreas, such as hardening of the head in chronic gallbladder disease, and up to the present we have not failed. We can say also, in many cases of cholecystitis without stone in which cholecystectomy has been done, that the symptoms in those persons are more due to hypopancreorrhea than to the gallbladder condition. Therefore, the field is a wide one, the usefulness of these findings is apparent, and again I make a plea that this test be used as a routine procedure which any one can do in forty minutes by simply following the schedule on that little rack, and I am sure that you will be as pleased as we are with the results accomplished.

BLOOD FIBRIN CHANGES IN VARIOUS DISEASES
WITH SPECIAL REFERENCE TO DISEASE
OF THE LIVER

JAMES S McLESTER, M.D.
MARION T DAVIDSON, M.D.
AND
BLANCHE FRAZIER

BIRMINGHAM, ALA

Foster and Whipple¹ have devised a relatively simple method for the clinical estimation of fibrinogen. In their experiments on animals, these investigators have found that fibrinogen, in direct contrast to the other blood proteins, varies widely in amount, and that the production of this labile protein is stimulated in different degrees by different diseases. Whipple concludes that the liver is the chief, if not the sole, source of fibrinogen, and finds that those diseases which stimulate or depress liver function in like manner and in equal degree stimulate or depress fibrinogen production.

This suggested to us the possible clinical value of a more comprehensive knowledge of the fibrin content of the blood in disease, especially in disease of the liver, and led us to undertake a series of fibrin estimations on the blood of patients and of normal people. These first observations were reported elsewhere.² Our fibrin studies have been continued, and we shall here report our findings in a series of a little over 200 persons. Eighteen of these were normal controls, and thirteen had definite disease of the liver.

We have prepared a few charts designed to show the fibrin content of the blood in a number of diseases. The figures express in milligrams the amount of fibrin in 100 c.c. of plasma.

Chart 1 shows the several determinations made on normal people. It was interesting to find that the same person in health shows at all times a surprisingly constant blood fibrin. It will be noted that while these values for different individuals as shown in this chart vary somewhat, on the whole they remain, during health, within fairly narrow limits. The values for blood fibrin in health range from 250 mg to 400 mg per hundred cubic centimeters of plasma, with an average of about 330 mg.

From these studies, we gather the following impressions:

1. The figures for each disease with a few exceptions appear to lie fairly close together.

2. Typhoid fever and grave anemias give low values.

1 Foster, D. P., and Whipple, G. H. Am J Physiol 58 365 (Jan.) 1922

2 McLester, J. S. Diagnostic Value of Blood Fibrin Determinations with Special Reference to Disease of the Liver, J. A. M. A. 79 17 (July 1) 1922

3 All other diseases, no matter of what nature (except when accompanied by great liver destruction), give increased fibrin values

4 Increased fibrin production bears no relation to the leukocyte count, for tuberculosis, chronic nephritis and myocardial disease all cause increased blood fibrin

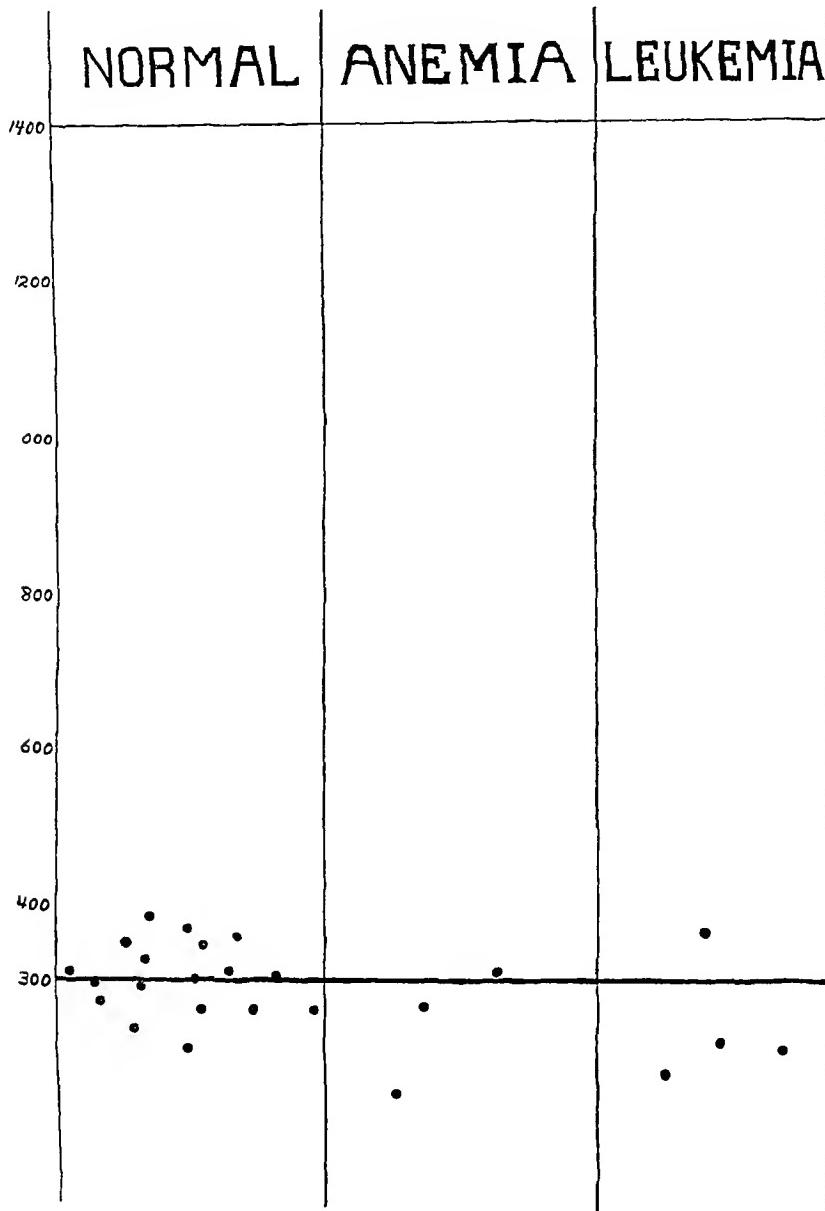


Chart 1—Normal values uniformly adhere to the base line, anemias and leukemias show a tendency to lie below this line

5 It is apparent that the extent and nature of the tissue injury—not an infecting organism—is the determining factor a sterile turpentine abscess is as effective in stimulating fibrinogen production as one of septic origin

6 The highest fibrin values are obtained in pneumonia and in septic states. Following the crisis in pneumonia or the drainage of an abscess however, there is an immediate fall in blood fibrin.

7 Regarding the liver, one can only confirm here the observation of Whipple made on experimental animals. He found that injury or

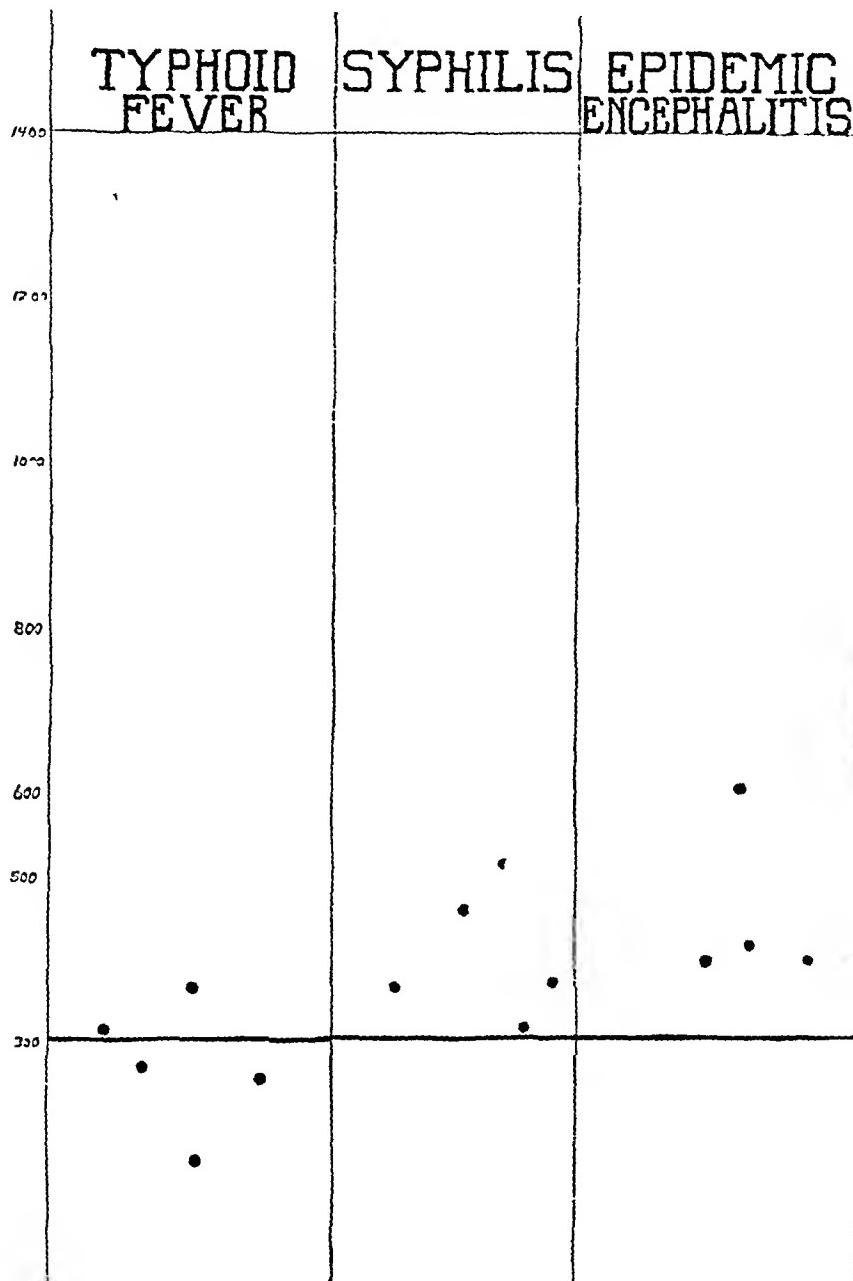


Chart 2.—The values for each disease as shown in this and the other charts lie fairly close together.

diseases which stimulate the liver are accompanied by increased blood fibrin, and that those which depress the liver or destroy a large part of its parenchyma lead to a very low blood fibrin. It would appear that the liver has a good factor of safety, and that a certain amount of its substance can be destroyed without loss of function.

The high blood fibrin seen in one instance was found in a patient who had carcinoma of the stomach with a large metastatic tumor in the liver. It is significant, however, that a preponderating amount of normal liver tissue remained. Since carcinoma in other locations stimulates fibrinogen production, and since this man retained a large amount of

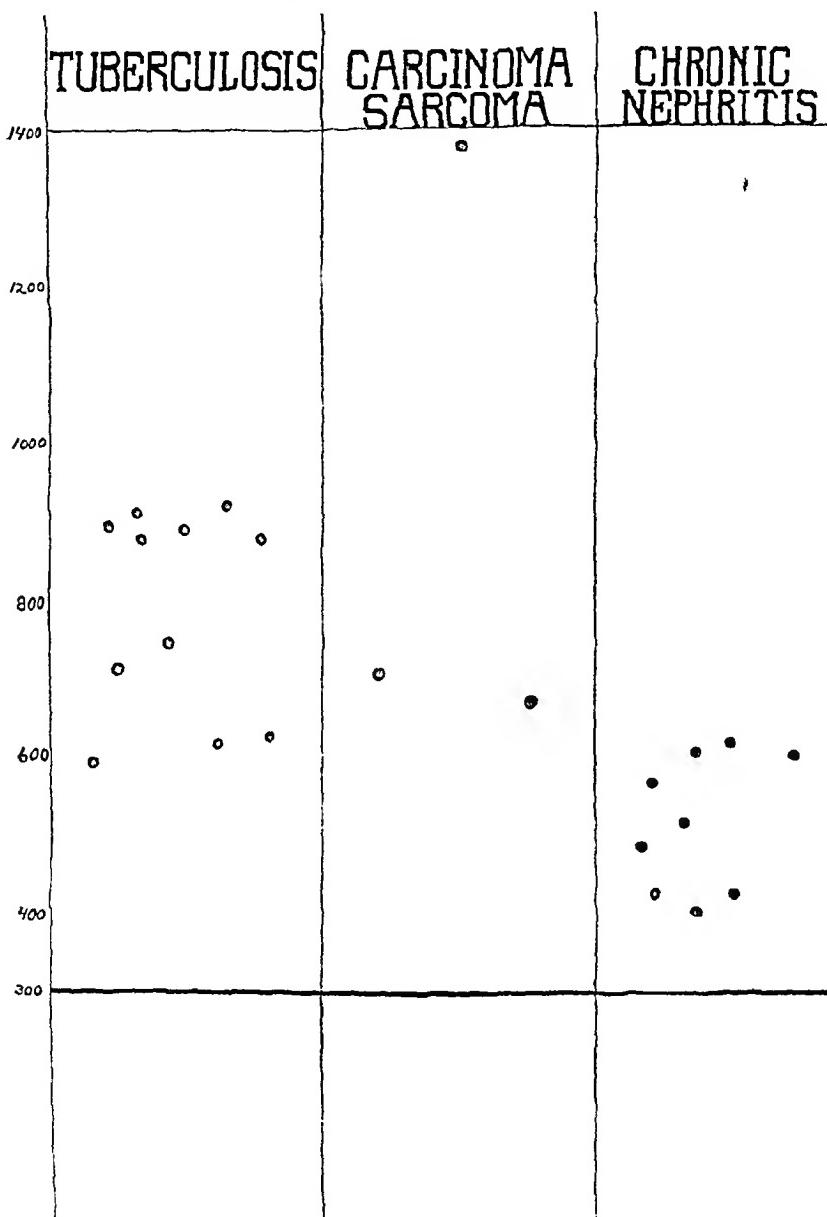


Chart 3.—Tuberculosis always shows definitely increased fibrin

apparently normal liver parenchyma, this marked increase in blood fibrin was the logical result. On the other hand, those patients with small cirrhotic livers give correspondingly low values.

It is especially significant that the second lowest blood fibrin of the entire series was found in a patient who, at necropsy, showed extensive

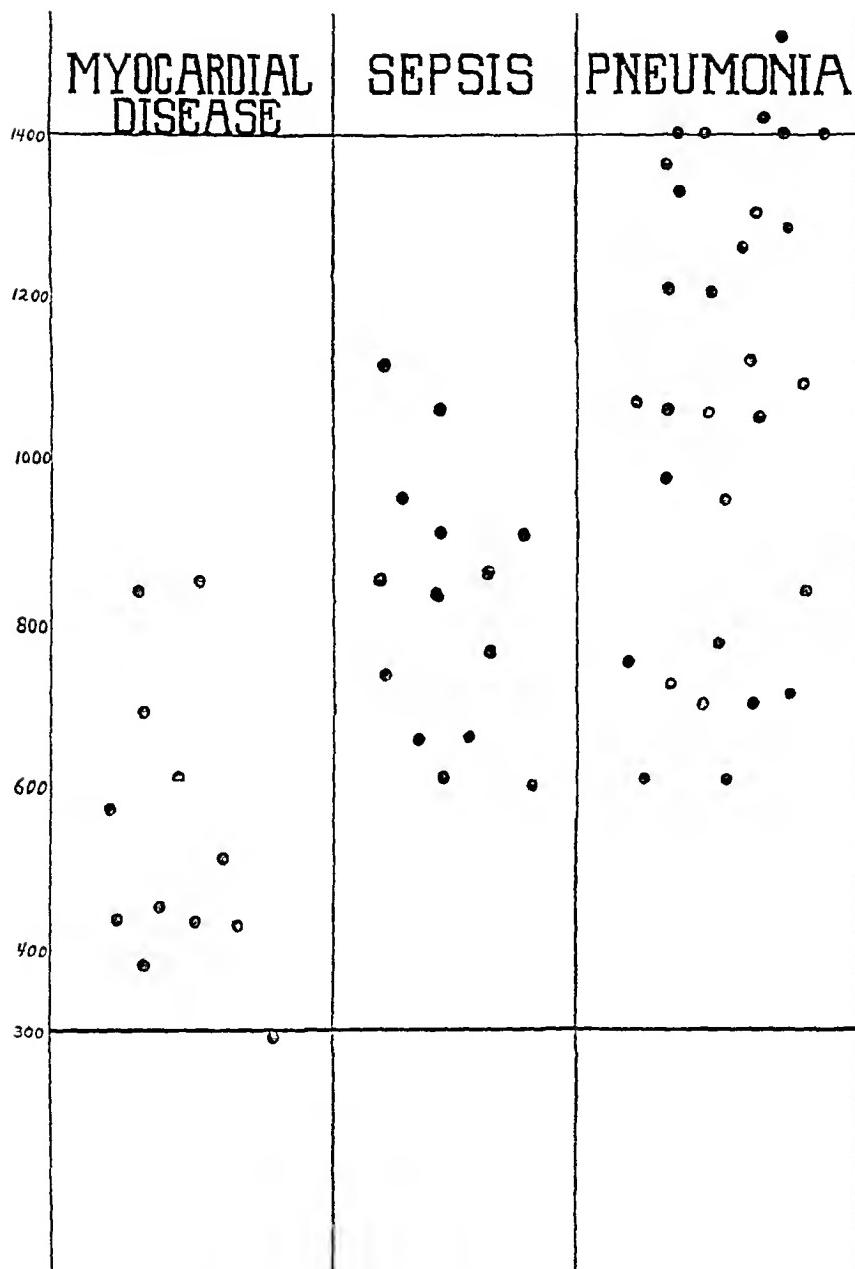


Chart 4.—High values in all septic states, especially high values in pneumonia

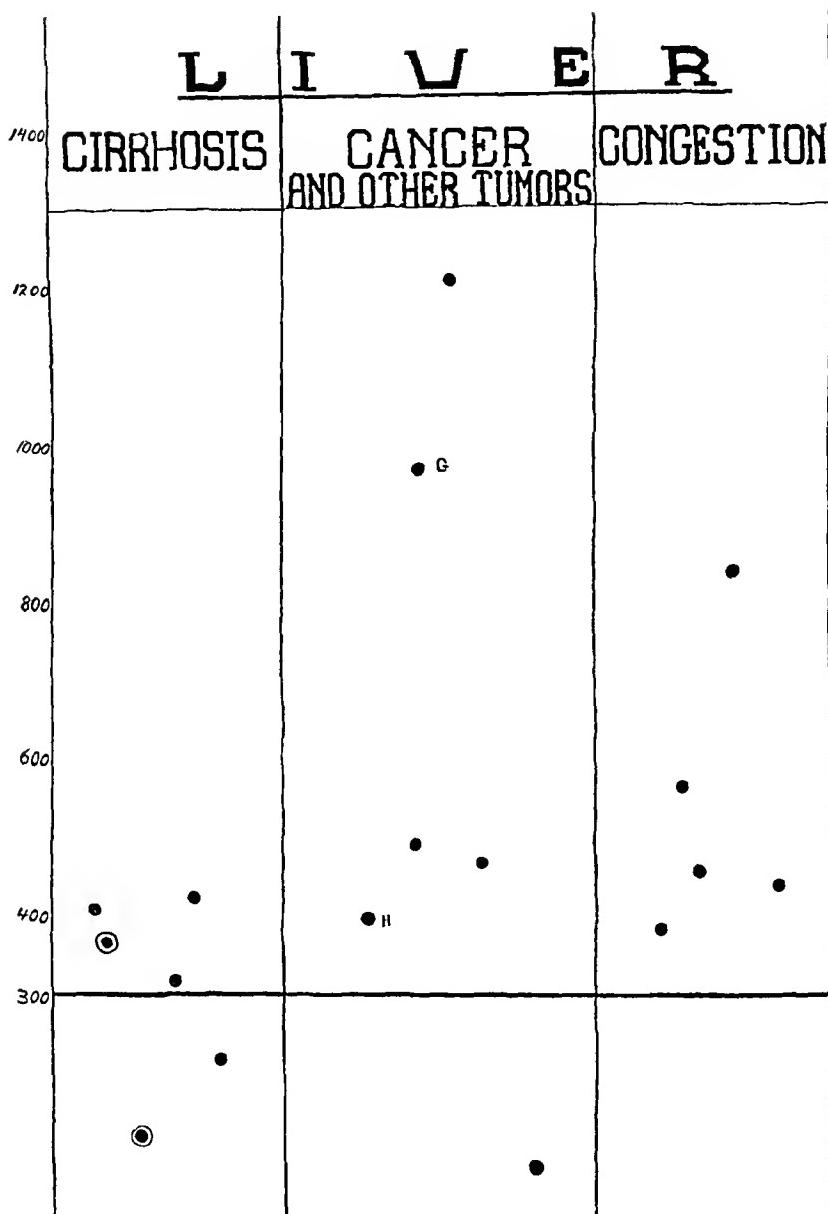


Chart 5.—Dots enclosed in a circle represent tuberculosis, one with a certain amount of cirrhosis, the other with almost complete destruction of liver substance, *G*, gastric carcinoma, *H*, Hodgkin's disease

tuberculous destruction of the liver. Very little parenchyma remained. It is noteworthy that while tuberculosis of the peritoneum or other organs causes increased fibrin production, the reverse is true and a very low blood fibrin is found when this same process destroys a material amount of liver parenchyma. One is tempted to generalize here and to conclude, therefore, that destruction of liver parenchyma leads to impairment of the mechanism by which the body produces fibrinogen.

CONCLUSION

We realize that these studies, as they stand today, do not point to anything of immediate diagnostic value. They do show, however, certain new and interesting facts. One of these is the general fact that blood fibrin varies markedly in disease, and that the direction and extent of this deviation from the normal depends on the nature of the pathologic process. It is not unreasonable, therefore, to hope that further more intensive studies may reveal other facts of direct clinical importance.

930 South Twentieth Street

STUDIES ON THE RESPIRATORY ORGANS IN HEALTH AND DISEASE

XIV THE VITAL CAPACITY OF THE LUNGS OF 419 FIREMEN *

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AND

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MINNEAPOLIS

The vital capacity of 419 Minneapolis firemen was secured in the present study. Of this number, 345 had been in the service of the fire department for a period of time ranging from three months to thirty-nine years and the remaining seventy-four were substitutes. The standing height was taken in every instance, the body weight was obtained in all but one man, the age in all but five, and the sitting height was secured in only 356 of the firemen. The men were all on active duty when they were measured. No sickness, either acute or chronic, was noted throughout the series.

TREATMENT OF THE DATA

Although the technical methods used in the collection of the data were accurate, the individual variability of the measurements taken was so large that the significance of the results could only be interpreted by the use of graphic and numerical analysis.

The order of procedure carried on in this study may be arranged in five groups: (1) the formation of tables showing the arithmetic averages together with the maximum and minimum values, (2) the construction of graphs showing the points of central tendency and the formation of empiric formulas by the method of weighted averages, (3) the calculation of the vital capacity and the computation of the absolute and percentage deviation of the calculated from the observed values, (4) the determination of the weighted average absolute and percentage deviants, and (5) the formation of secondary tables to show the relative increase or decrease of vital capacity.

1 The Formation of Tables Showing the Arithmetic Averages Together with the Maximum and Minimum Values—Tables were made in which the vital capacity was grouped successively with the body length, stem length, body weight, age and the length of service. Field graphs

* Presented, in part, before the medical staffs of the Lymanhurst School for Tuberculous Children and the Parkview Sanatorium, June 24, 1924.

From the department of internal medicine and the department of preventive medicine and public health, University of Minnesota Medical School.

This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

were plotted, in each instance for which the vital capacity was used for the ordinate and the respective linear, temporal or ponderal determination for the abscissa. When body length or stem length were used for the abscissa, the material was divided into intervals of one-half and one-quarter inches, respectively; when age or length of service was employed, the data were arranged by yearly increments, and when body weight represented the X axis, the data were grouped into 5 pound (2.3 kg.) intervals. The weighted arithmetic average was then obtained in each group by averaging both the X and the Y values in the respective intervals. The maximum and minimum values of the vital capacity were also recorded together with the mean.

2 The Construction of Graphs Showing the Points of Central Tendency and the Formation of Empiric Formulas by the Method of Weighted Averages—Graphs were constructed showing the general curve of the central tendency by first plotting the average vital capacities. From these averages, empiric formulas were obtained. A general inspection of the field graphs and the average points led to the assumption that an expression of the central tendency of the data could be best obtained by a straight line formula. In order to secure the best straight line formula, the method of averages was used. The general formula for a straight line is expressed by the equation $Y = a + bX$, in which Y and X are variables and a and b are known constants. The method of averages facilitates the calculation of the constants, a and b . In order to evaluate the constants, a and b , for any given equation, the data should be divided into two equal parts, explained, in Lipka,¹ “place the sum of the residuals in each group equal to zero, i.e.,

$$\Sigma (1 - a - bc) = 0$$

which is equal to $\Sigma r = na + b\Sigma c$ where n is the number of observations in the group.” In calculating the equation for vital capacity against standing height, for instance, the data were divided into two groups, each containing half the total number of cases. The sum of the vital capacities (ΣY) and the sum of the body length (ΣX) were computed for each group of cases. When these equations were solved simultaneously, the values of the constants a and b were determined.

Since the numbers of cases were bunched unequally throughout this series, another step was introduced in the formation of the equations. The averages were weighted by multiplying the mean by the number of cases. In this manner, the significance of an average based on one or two cases was reduced to the same proportion as those averages calculated from many cases.

¹ Lipka, Graphical and Mechanical Computation, New York, John Wiley & Sons, 1918, p. 126.

3 The Calculation of Vital Capacity and the Computation of the Absolute and the Percentage Deviations of the Calculated from the Observed Values—After the formulas were obtained, the vital capacity

TABLE 1—*Observed Vital Capacity of 419 Enlisted Men Ranging in Standing Height from 63 to 78 Inches (160 to 198.1 cm)*

Standing Height, Inches		Num ber of Cases	Body Weight, Pounds	Age, Years	Vital Capacity, C c			Length of Service, Years		Sitting Height, Inches	
Range	Mean				Maxi- mum	Min- imum	Mean	No. of Cases	Mean	No. of Cases	Mean
63 0-63 5	63.3	1	139.0	61.0	3,500	3,500	3,500	1	33.0	1	33.0
63 5-64 0											
64 0-64 5											
64 5-65 0	64.5	1	133.0	61.0	4,000	4,000	4,000	1	33.0	1	33.0
65 0-65 5	65.2	1	169.0	46.0	3,850	3,850	3,850	1	21.0	1	33.3
65 5-66 0	65.8	2	165.0	39.0	3,950	3,500	3,725	2	25.5	2	33.4
66 0-66 5	66.2	12	169.8	38.7	4,350	2,900	3,692	8	11.1	9	34.5
66 5-67 0	66.6	17	163.6	40.7	4,600	2,800	3,781	17	13.3	17	34.4
67 0-67 5	67.1	33	169.7	40.9	4,800	2,900	3,953	30	14.9	30	34.8
67 5-68 0	67.6	32	170.1	37.2	5,200	3,200	4,163	27	10.7	27	34.9
68 0-68 5	68.1	27	175.1	37.3	5,750	2,800	4,246	24	11.3	24	35.2
68 5-69 0	68.6	49	170.6	37.6	5,750	3,000	4,332	37	11.2	38	35.1
69 0-69 5	69.1	40	169.4	34.1	5,650	3,300	4,639	30	9.6	32	35.4
69 5-70 0	69.6	51	182.2	36.9	5,350	3,050	4,459	44	10.9	45	35.7
70 0-70 5	70.1	39	180.6	37.4	5,800	3,250	4,484	31	10.4	31	35.9
70 5-71 0	70.6	28	185.5	40.5	5,750	3,500	4,556	24	15.5	26	35.6
71 0-71 5	71.1	21	185.0	34.4	5,750	3,500	4,798	14	11.3	15	36.4
71 5-72 0	71.6	18	184.2	32.8	6,300	3,600	4,719	13	8.0	14	36.3
72 0-72 5	72.1	12	188.3	39.4	5,600	4,200	4,696	11	11.5	12	36.8
72 5-73 0	72.6	11	198.0	35.7	5,650	3,600	4,741	8	14.0	9	36.2
73 0-73 5	73.0	8	184.3	30.1	6,250	4,250	5,488	7	7.4	8	35.9
73 5-74 0	73.6	5	222.4	41.4	5,650	4,700	5,120	3	16.3	3	37.8
74 0-74 5	74.0	2	204.5	34.0	5,000	4,700	5,300	2	7.2	2	37.9
74 5-75 0	74.6	2	213.5	40.0	5,650	5,650	5,650	2	13.0	2	38.6
75 0-75 5	75.0	3	208.3	44.0	6,150	5,000	5,450	3	16.3	3	37.8
75 5-76 0											
76 0-76 5											
76 5-77 0	76.8	1	225.0	31.0	4,250	4,250	4,250	1	9.0	1	37.7
77 0-77 5	77.3	1	210.0	31.0	5,100	5,100	5,100	1	13.0	1	38.5
77 5-78 0	77.6	2	208.0	40.0	6,950	5,300	6,125	2	11.5	2	39.5

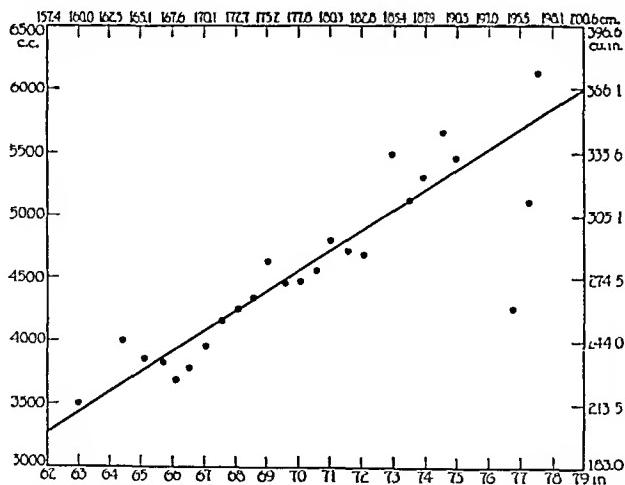


Fig. 1.—Relation between average vital capacity and standing height

was calculated at each average point. The absolute deviation of the calculated from the observed value was then obtained and noted in tabular form. The percentage which the absolute deviant formed of the

observed value was then determined. In this way, the accuracy of the formula was estimated for each average value.

4 The Determination of the Weighted Average Absolute and Percentage Deviants—The absolute and percentage deviants were weighted by multiplying them by the number of cases which they represented. These weighted deviants were then averaged by first adding them together and then dividing by the total number of cases. The average weighted deviants resulting from this procedure express the accuracy of the formula. Since all formulas were obtained in a mathematical manner, the weighted average deviants are a measure of the importance of the various factors with which vital capacity is correlated.

5 The Formation of Secondary Tables to Show the Relative Increase or Decrease of the Vital Capacity—The values of vital capacity were computed at regular intervals of time, length and weight. The absolute increments, the percentage increments and the percentage of the total increments for these intervals were then determined. The absolute increment represents the increase in cubic centimeters of the vital capacity for a stated unit of time, of length or of weight. A decrease of the vital capacity is a negative increment. The percentage increment is calculated by determining the percentage which the increment for any interval forms of the absolute value at the beginning of the interval. In order to determine how much of the total increase or decrease in vital capacity has occurred at any definite interval of length, weight or time, the percentage of the total increment was also calculated.

COMMENT ON RESULTS

Vital Capacity in Relation to Standing Height—Vital capacity increases at a steady rate as the body length becomes larger (Table 1, Chart 1), and it may be expressed by the empiric formula:

$$\text{Vital capacity (cubic centimeters)} = 159.9 \text{ body length (inches)} - 6,655$$

The absolute vital capacity at a body length of 63 inches (160 cm) is 3,419 c.c. This rapidly increases to 5,817 c.c. at a standing height of 78 inches (198.1 cm), or approximately, 160 c.c. for every inch of stature (Table 3).

As the standing height becomes greater, the body weight and the sitting height also increase in size. The age and the length of service, however, do not vary to any extent in the taller individuals.

The range of variability of the data is expressed in a rough way by the maximum and minimum values (Table 1 Chart 2). Although these quantities show a wide variation they both increase with the

TABLE 2—*Observed and Calculated Vital Capacity of 419 Frenchmen Ranging in Standing Height from 63 to 78 Inches (160 to 198.1 cm.)*

Standing Height, Inches	Mean	Observed Mean Vital Capacity Cc	Calculated Vital Capacity Cc	Deviation of Calculated from Observed Values	
				Cubic Centimeters	Per Cent
Range	Mean				
63 0-63 5	63.3	3,600	3,467	- 33	- 0.94
63 5-64 0					
64 0-64 5					
64 5-65 0	64.5	4,000	3,659	- 341	- 8.53
65 0-65 5	65.2	3,850	3,770	- 80	- 2.08
65 5-66 0	65.8	3,725	3,866	+ 141	+ 3.79
66 0-66 5	66.2	3,692	3,930	+ 238	+ 6.45
66 5-67 0	66.6	3,781	3,894	+ 213	+ 5.63
67 0-67 5	67.1	3,953	4,074	+ 121	+ 3.06
67 5-68 0	67.6	4,163	4,154	- 9	- 0.22
68 0-68 5	68.1	4,246	3,234	- 12	- 0.28
68 5-69 0	68.6	4,332	4,314	- 18	- 0.42
69 0-69 5	69.1	4,639	4,394	- 245	- 5.8
69 5-70 0	69.6	4,459	4,474	+ 15	+ 0.34
70 0-70 5	70.1	4,484	4,554	+ 70	+ 1.56
70 5-71 0	70.6	4,556	4,634	+ 78	+ 1.71
71 0-71 5	71.1	4,798	4,714	- 84	- 1.75
71 5-72 0	71.6	4,719	4,794	+ 75	+ 1.59
72 0-72 5	72.1	4,696	4,874	+ 178	+ 3.79
72 5-73 0	72.6	4,741	4,934	+ 213	+ 4.49
73 0-73 5	73.0	5,488	5,018	- 470	- 8.56
73 5-74 0	73.6	5,120	5,114	- 6	- 0.12
74 0-74 5	74.0	5,300	5,178	- 122	- 2.30
74 5-75 0	74.6	5,650	5,274	- 376	- 6.65
75 0-75 5	75.0	5,450	5,388	- 112	- 2.06
75 5-76 0					
76 0-76 5					
76 5-77 0	76.8	4,250	5,625	+1,375	+32.35
77 0-77 5	77.3	5,100	5,705	+ 605	+11.86
77 5-78 0	77.6	6,125	5,753	- 372	- 6.07

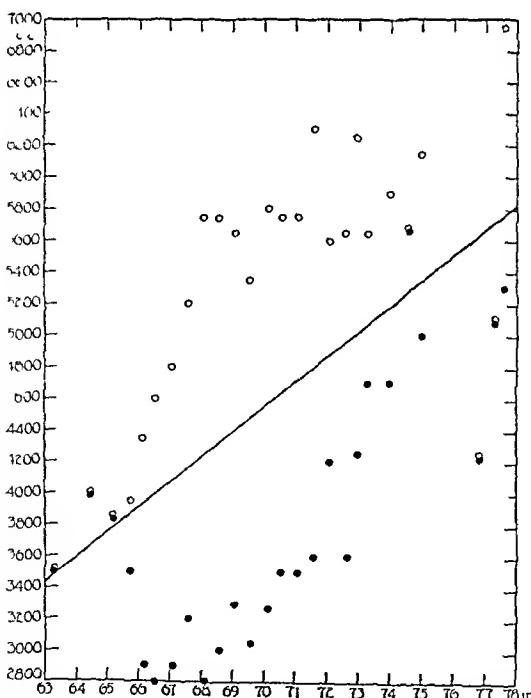


Fig 2.—Relation between maximum and minimum vital capacity values and standing height

growth in body length. The range of variability is approximately from one eighth to one sixth of the calculated values on each side of the curve of the central tendency.

The absolute and percentage deviants of the calculated from the observed averages (Table 2) are not unusually large except in one instance. In this case, a deviation of 30 per cent is due to an average based on only one case.

TABLE 3.—*Changes in Calculated Vital Capacity of 419 Firemen Ranging in Standing Height from 63 to 78 Inches (160 to 198.1 cm.)*

Standing Height, Inches	Calculated Vital Capacity, Cc	Increment		Percentage of Total Increment
		Cubic Centimeters	Percentage	
63	3.419			
64	3.579	160	4.680	6.67
65	3.739	160	4.471	13.84
66	3.898	159	4.252	19.98
67	4.058	160	4.105	26.65
68	4.218	160	3.943	33.32
69	4.378	160	3.793	39.99
70	4.538	160	3.655	46.66
71	4.698	160	3.526	53.34
72	4.858	160	3.406	60.01
73	5.018	160	3.294	66.68
74	5.178	160	3.189	73.35
75	5.338	160	3.080	80.02
76	5.497	159	2.979	86.66
77	5.657	160	2.911	93.33
78	5.817	160	2.828	100.00

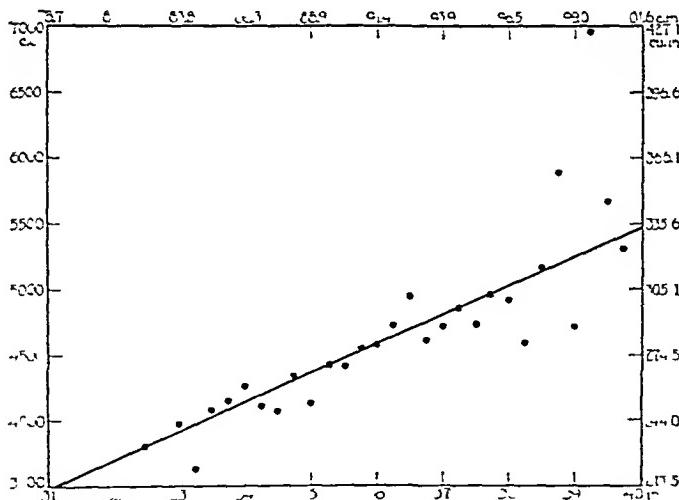


Fig. 3.—Relation between average vital capacity and sitting height

The weighted average deviants of the vital capacity-standing height relationship are expressed in Table 16. The weighted average absolute deviant is 104.1 c.c., and the weighted average percentage deviant, 2.33 per cent. This low deviation tends to prove that a close correlation exists between vital capacity and standing height, which is more accurate than the correlation of vital capacity with any other body measurements considered in this study.

TABLE 4—*Observed Vital Capacity of 356 Firemen Ranging in Sitting Height from 32 to 40 Inches (81.2 to 101.6 cm.)*

Mean Sitting Height, Inches	Num ber of Cases	Standing Height, Inches	Body Weight, Pounds	Length of Service, Years	Age, Years	Vital Capacity C.c.		
						Maximum	Minimum	Mean
32.00	1	67.5	148.0	25.0	55.0	4,475	4,475	4,475
32.25								
32.50	1	66.0	184.0	12.0	35.0	3,700	3,700	3,700
32.75								
33.00	6	67.6	144.6	13.4	36.5	4,650	3,000	3,983
33.25	2	66.4	157.0	14.0	40.5	3,850	3,200	3,525
33.50	3	67.3	144.6	21.0	50.0	4,300	3,500	4,016
33.75	11	67.9	169.0	15.1	41.1	5,500	3,500	4,136
34.00	20	68.2	159.7	13.0	39.0	5,400	2,900	4,025
34.25	17	67.6	166.6	12.8	41.2	5,150	2,900	4,100
34.50	21	68.4	171.1	14.7	40.4	5,750	3,150	4,057
34.75	18	68.5	167.8	9.8	37.0	4,950	3,200	4,819
35.00	31	68.4	168.8	11.8	39.6	5,650	3,250	4,111
35.25	22	69.1	172.7	13.7	39.6	5,350	3,150	4,405
35.50	36	69.6	179.9	12.0	36.8	6,000	2,900	4,889
35.75	29	69.0	179.0	9.7	36.8	5,750	3,300	4,546
36.00	32	69.4	179.0	9.5	33.3	5,750	2,900	4,566
36.25	25	70.1	176.0	10.7	34.4	5,500	3,700	4,712
36.50	14	70.3	188.9	9.4	33.6	6,250	3,850	4,929
36.75	14	71.0	186.9	15.8	42.4	5,600	3,500	4,596
37.00	26	71.2	203.6	12.2	36.9	5,800	3,860	4,702
37.25	4	71.6	190.8	13.9	40.7	5,800	4,150	4,888
37.50	5	71.6	194.0	13.3	39.8	5,400	4,250	4,710
37.75	2	74.7	201.5	7.0	31.5	5,650	4,250	4,050
38.00	6	71.4	199.5	7.5	35.6	5,700	3,950	4,900
38.25	2	69.9	213.5	7.7	37.0	4,750	4,400	4,575
38.50	2	70.1	196.0	10.0	40.5	5,200	5,100	5,150
38.75	2	74.5	195.5	7.7	31.5	6,150	5,900	6,025
39.00	1	73.5	280.0	9.0	29.0	4,700	4,700	4,700
39.25	1	77.8	195.0	4.5	34.0	6,950	6,950	6,950
39.50	1	74.8	216.0	9.0	30.0	5,650	5,650	5,650
39.75	1	77.5	221.0	18.5	46.0	5,300	5,300	5,300

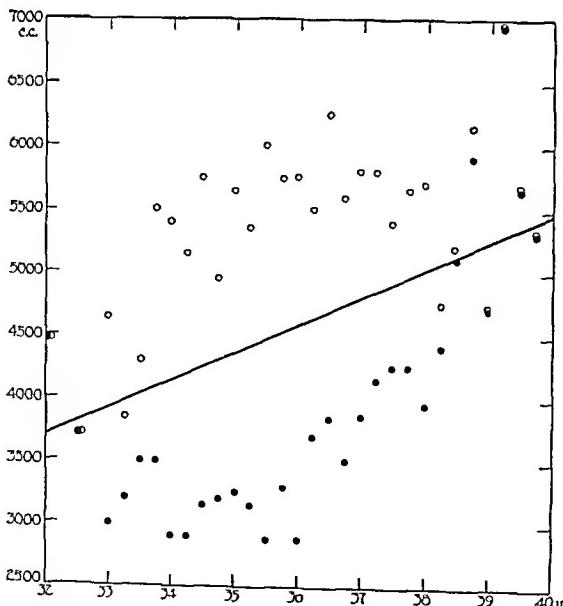


Fig 4.—Relation between maximum and minimum vital capacity values and sitting height

Although the absolute increase in vital capacity is about 160 cc for each additional inch of body length (Table 3), the percentage increment or rate of increase per inch steadily falls from about 47 per cent between the body lengths from 63 to 64 inches (160 to 162.5 cm) to about 28 per cent between 77 and 78 inches (195.6 to 198.1 cm).

TABLE 5—*Observed and Calculated Vital Capacity of 356 Firemen Ranging in Sitting Height from 32 to 40 Inches (81.2 to 101.6 cm)*

Mean Sitting Height, Inches	Observed Mean Vital Capacity, cc	Calculated Vital Capacity, cc	Deviation of Calculated from Observed Values	
			Cubic Centimeters	Per Cent
32.00	4,475	3,706	— 769	-17.18
32.25				
32.50	3,700	3,815	+ 115	+ 3.11
32.75				
33.00	3,983	3,925	- 58	- 1.46
33.25	3,525	3,979	+ 454	+12.88
33.50	4,016	4,034	+ 18	+ 0.45
33.75	4,136	4,089	- 47	- 1.14
34.00	4,025	4,144	+ 119	+ 2.96
34.25	4,100	4,198	+ 98	+ 2.39
34.50	4,057	4,258	+ 196	+ 4.83
34.75	4,819	4,308	- 11	- 0.25
35.00	4,111	4,363	+ 252	+ 6.13
35.25	4,405	4,417	+ 12	+ 0.27
35.50	4,389	4,472	+ 83	+ 1.89
35.75	4,546	4,527	- 19	- 0.42
36.00	4,566	4,581	+ 15	+ 0.33
36.25	4,712	4,636	- 76	- 1.61
36.50	4,929	4,691	- 238	- 4.83
36.75	4,596	4,746	+ 150	+ 3.26
37.00	4,702	4,800	+ 98	+ 2.08
37.25	4,838	4,855	+ 17	+ 0.35
37.50	4,710	4,910	+ 200	+ 4.25
37.75	4,950	4,964	+ 14	+ 0.28
38.00	4,900	5,019	+ 119	+ 2.43
38.25	4,575	5,074	+ 499	+10.91
38.50	5,150	5,129	- 21	- 0.41
38.75	6,025	5,183	- 832	-13.81
39.00	4,700	5,238	+ 538	+11.45
39.25	6,950	5,293	-1,657	-23.84
39.50	5,650	5,348	- 302	- 5.35
39.75	5,300	5,402	+ 102	+ 1.92

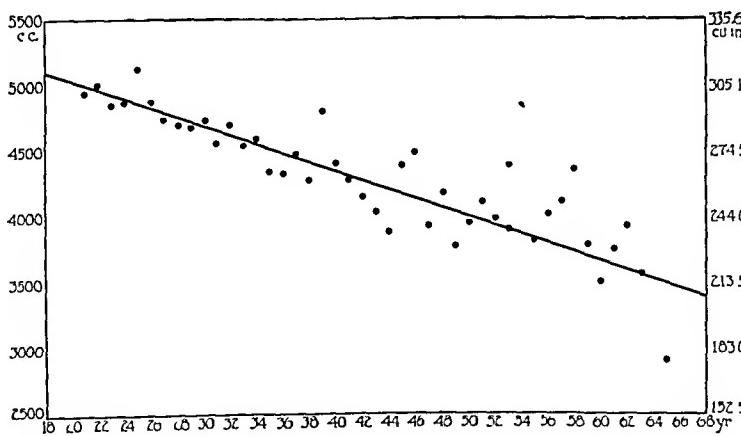


Fig. 5—Relation between average vital capacity and age

Twenty-five per cent of the total increase in vital capacity between the standing heights of 63 to 78 inches (160 to 198.1 cm) has taken place at a stature of 67 inches (170.2 cm), 50 per cent at a body length of 71 inches (180.3 cm) and 75 per cent at 74 inches (188 cm).

Vital Capacity in Relation to Sitting Height—Vital capacity progresses at a steady rate in unison with an increase in sitting height (Table 4, Chart 3) The growth of vital capacity in terms of stem length may be expressed by the empiric formula

$$\text{Vital capacity (cubic centimeters)} = 218.9 \text{ body length (inches)} - 3,299$$

TABLE 6—Changes in Calculated Vital Capacity of 356 Females Ranging in Sitting Height from 32 to 40 Inches (81.2 to 101.6 cm.)

Sitting Height, Inches	Calculated Vital Capacity, cc	Increment		Percentage of Total Increment
		Cubic Centimeters	Percentage	
32	3,706			
33	3,925	219	5.909	12.51
34	4,144	219	5.580	25.01
35	4,363	219	5.285	37.52
36	4,581	219	4.997	49.97
37	4,800	219	4.781	62.48
38	5,019	219	4.562	74.99
39	5,238	219	4.363	87.49
40	5,457	219	4.181	100.00

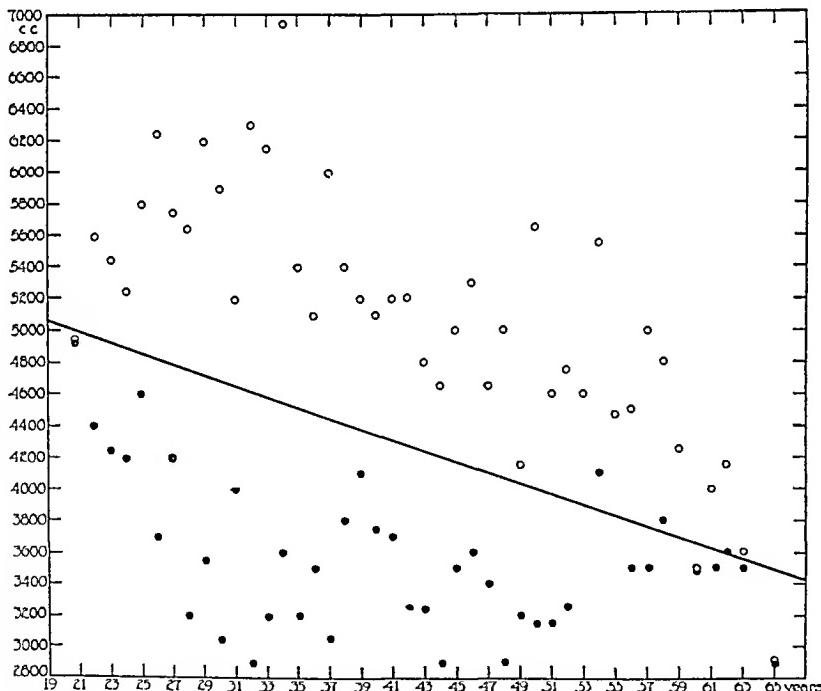


Fig 6.—Relation between maximum and minimum vital capacity values and age

The absolute vital capacity grows steadily larger from 3,706 cc at 32 inches (81.2 cm) sitting height to 5,457 cc at 40 inches (101.6 cm)—an increase of 219 cc per inch (Table 6)

As the stem length increases, the body weight and the standing height likewise grow larger. Age and length of service, however, are practically unchanged as the sitting height becomes longer.

TABLE 7—*Observed Vital Capacity of 414 Firemen Ranging in Age from 21 to 65 Years*

Age, Years	Num ber of Cases	Body Weight, Pounds	Standing Height, Inches	Vital Capacity Cc			Length of Service, Sitting Height, Years		Sitting Height, Inches	
				Maxi- mum	Mini- mum	Mean	No. of Cases	Mean	No. of Cases	Mean
21	1	149.0	70.3	4,950	4,950	4,950	1	1.0	1	36.7
22	2	169.0	72.0	5,600	4,400	5,000	1	0.3	2	36.1
23	2	138.0	72.0	5,450	4,250	4,850			2	35.0
24	3	166.3	69.4	5,250	4,200	4,867			3	35.8
25	8	158.8	69.1	5,800	4,600	5,125	5	4.5	5	36.1
26	21	173.3	69.5	6,250	3,700	4,874	18	4.6	18	35.6
27	19	178.1	69.8	5,750	4,200	4,743	16	4.9	17	35.7
28	27	171.9	69.5	5,650	3,200	4,706	21	5.1	22	35.3
29	28	178.3	69.7	6,200	3,550	4,671	24	5.4	24	36.0
30	26	178.7	69.7	5,900	3,050	4,735	21	5.7	22	35.9
31	14	182.0	70.6	5,200	4,000	4,564	14	4.9	14	35.5
32	24	183.4	69.9	6,300	2,800	4,693	14	6.5	14	35.8
33	18	172.5	68.7	6,150	3,200	4,542	15	6.2	16	35.7
34	15	173.0	69.9	6,950	3,000	4,590	14	6.3	14	35.8
35	26	172.9	68.8	5,400	3,200	4,343	21	9.0	22	35.2
36	11	176.2	69.2	5,100	3,500	4,336	10	8.0	10	35.0
37	11	178.5	69.4	6,000	3,058	4,473	7	7.5	7	35.3
38	10	186.5	69.4	5,400	3,800	4,283	9	12.1	9	35.7
39	3	171.0	72.1	5,200	4,100	4,800	2	13.5	2	37.0
40	6	178.5	69.1	5,100	3,750	4,408	6	13.5	6	36.0
41	6	204.6	68.7	5,200	3,700	4,223	6	13.3	6	35.8
42	11	179.7	69.5	5,200	3,250	4,150	10	14.1	10	35.7
43	8	158.6	68.4	4,800	3,250	4,044	7	17.0	7	35.2
44	10	183.9	68.3	4,650	2,900	3,890	9	17.8	9	35.2
45	6	206.7	69.7	5,000	3,500	4,883	4	14.8	4	36.7
46	10	215.2	69.9	5,300	3,600	4,482	8	17.9	8	35.8
47	5	188.6	69.6	4,650	3,400	3,920	5	14.7	5	35.7
48	9	180.2	68.8	5,000	2,900	4,189	8	18.8	8	35.6
49	5	176.6	68.9	4,150	3,200	3,770	2	18.8	2	34.7
50	10	195.4	69.1	5,650	3,150	3,950	9	18.9	9	35.6
51	10	183.3	69.5	4,600	3,150	4,105	9	22.3	9	35.6
52	7	172.1	68.6	4,750	3,250	3,971	7	25.6	7	34.9
53	6	171.2	69.3	4,000	2,800	3,908	5	22.4	5	35.0
54	2	219.0	71.0	5,550	4,100	4,825	2	22.0	2	36.0
55	4	178.0	68.1	4,475	2,900	3,819	3	24.0	3	33.8
56	5	171.2	69.0	4,500	3,500	4,010	5	29.2	5	35.3
57	4	187.8	70.1	5,000	3,500	4,112	4	24.5	4	35.6
58	3	167.0	69.7	4,800	3,800	4,350	2	16.4	2	35.1
59	5	185.4	69.0	4,250	2,900	3,780	5	31.6	5	35.4
60	2	167.0	69.4	3,500	3,500	3,500	2	28.5	2	36.4
61	4	164.8	66.7	4,000	3,500	3,750	3	31.7	3	34.1
62	3	184.3	69.2	4,150	3,600	3,933	3	32.3	3	35.4
63	3	195.7	70.1	3,600	3,500	3,567	3	35.0	3	34.7
64										
65	1	202.0	66.0	2,900	2,900	2,900	1	24.0	1	34.3

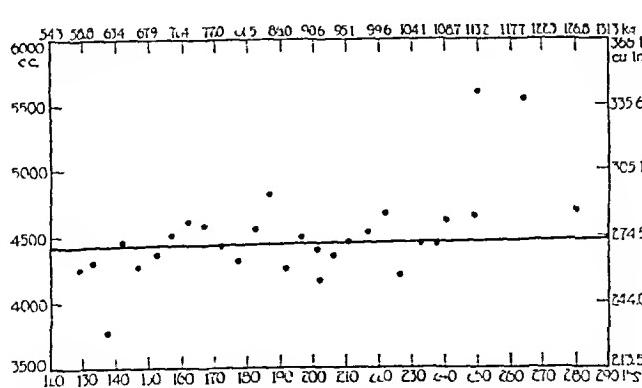


Fig. 7.—Relation between average vital capacity and body weight

The range of variability, as shown by the maximum and the minimum values (Table 4, Chart 4), shows a wide variation. Both the maximum and minimum values increase with a growth in the stem length. The range of variability is about one eighth to one sixth of the calculated values on both sides of the central tendency curve.

The absolute and percentage deviations of the calculated from the observed averages are shown in Table 5. In the case of six average points in this table, the percentage deviations are more than 10 per cent. In all of them, however, the cases from which the averages were obtained numbered only one or two.

The weighted average deviants of the vital capacity-stem length formula are expressed in Table 16. The weighted average absolute deviant is 112.8 cc and the weighted average percentage deviant, 2.53 per cent, this shows a close correlation between vital capacity and stem length. It was not possible, however, to fit the data quite so closely to the empiric formula as in the case of the body length.

The percentage increment or the rate of increase in the vital capacity grows steadily less as the stem length becomes longer (Table 6). The percentage increment is about 5.9 per cent between a sitting height of from 32 to 33 inches (81.2 to 82.8 cm) and falls to 4.2 per cent between 39 and 40 inches (98.5 and 101.6 cm).

Twenty-five per cent of the total increase in vital capacity between the stem length from 32 to 40 inches (81.2 to 101.6 cm) occurs at a sitting height of 34 inches (86 cm), 50 per cent at a height of 36 inches (91.4 cm) and 75 per cent at 38 inches (96.4 cm).

Vital Capacity in Relation to Age—Vital capacity decreases steadily as the age of an individual becomes greater (Table 7, Chart 5). It may be expressed by the empiric formula:

$$\text{Vital capacity (cubic centimeters)} = 5,725 - 34.46 \text{ times age (years)}$$

The absolute vital capacity decreases steadily from 5,036 cc at 20 years to 3,485 cc at 65 years, or approximately 172 cc every five years (Table 9).

As the age becomes greater, the standing and the sitting heights of the individuals in this series remains about the same. Vital capacity increases very rapidly with standing height and stem length. On the other hand, it decreases with advancing age. Since the relationship between standing height or sitting height and age remains practically unchanged, at least two factors must influence the vital capacity (1) the growth of the lungs, and (2) the loss in elasticity of the alveolar walls. The increase of vital capacity in relation to a growth in body length and stem length is undoubtedly due to an actual growth of the lung while the decline of vital capacity with age is due in all probability

TABLE 8—*Observed and Calculated Vital Capacity of 414 Firemen Ranging in Age from 21 to 65 Years*

Mean Age, Years	Observed Mean Vital Capacity, Cc	Calculated Vital Capacity, Cc	Deviation of Calculated from Observed Values	
			Cubic Centimeters	Per Cent
21	4,950	5,001.3	+ 51.3	+ 1.04
22	5,000	4,966.9	- 33.1	- 0.66
23	4,850	4,932.4	- 82.4	- 1.70
24	4,867	4,895.0	- 31.0	- 0.64
25	5,125	4,863.5	- 261.5	- 5.10
26	4,874	4,829.0	- 45.0	- 0.92
27	4,743	4,794.6	- 51.6	+ 1.00
28	4,706	4,760.1	- 54.1	+ 1.15
29	4,671	4,725.7	+ 54.7	- 1.17
30	4,735	4,691.2	- 43.8	- 0.93
31	4,561	4,656.7	- 92.7	+ 2.03
32	4,693	4,622.3	- 70.7	- 1.51
33	4,542	4,587.8	+ 45.8	+ 1.01
34	4,590	4,553.4	- 36.6	- 0.80
35	4,843	4,518.9	- 175.9	+ 4.05
36	4,836	4,484.4	- 148.4	+ 3.42
37	4,473	4,450.0	- 23.0	- 0.51
38	4,285	4,415.5	- 130.5	+ 3.05
39	4,800	4,381.1	- 118.9	- 8.73
40	4,405	4,316.6	- 61.4	- 1.39
41	4,283	4,312.1	- 29.1	- 0.68
42	4,150	4,277.7	+ 127.7	+ 3.08
43	4,014	4,243.2	- 199.2	- 4.92
44	3,890	4,208.8	- 318.8	+ 8.20
45	4,883	4,174.3	- 205.7	- 4.76
46	4,482	4,189.8	- 342.2	- 7.63
47	3,920	4,105.4	- 185.4	+ 4.73
48	4,189	4,070.9	- 118.1	- 2.82
49	3,770	4,036.5	+ 266.5	+ 7.07
50	3,950	4,002.0	- 52.0	+ 1.32
51	4,105	3,907.5	- 137.5	- 3.35
52	3,971	3,933.1	- 37.9	- 0.95
53	3,905	3,898.6	- 9.4	- 0.24
54	4,825	3,864.2	- 960.8	- 19.91
55	3,819	3,829.7	- 10.7	+ 0.28
56	4,010	3,795.2	- 214.8	- 5.36
57	4,112	3,760.8	- 351.2	- 8.54
58	4,350	3,726.3	- 623.7	- 14.34
59	3,780	3,691.9	- 88.1	- 2.33
60	3,500	3,657.4	+ 157.4	- 4.48
61	3,750	3,622.9	- 127.1	- 3.39
62	3,933	3,588.5	- 344.5	- 8.76
63	3,567	3,554.0	- 13.0	- 0.36
64			3,519.6	
65	2,900	3,485.1	+ 585.1	+20.18

TABLE 9—*Changes in Calculated Vital Capacity of 414 Firemen Ranging in Age from 20 to 65 Years*

Age, Years	Calculated Vital Capacity, Cc	Decrement		Percentage of Total Decrease
		Cubic Centimeters	Percentage	
20	5,036			
25	4,864	-172	-3.415	+ 11.09
30	4,691	-173	-3.557	- 22.24
35	4,519	-172	-3.667	+ 33.33
40	4,347	-172	-3.806	- 44.42
45	4,174	-173	-3.950	+ 55.58
50	4,002	-172	-4.121	+ 66.67
55	3,830	-172	-4.298	+ 77.75
60	3,657	-173	-4.517	+ 88.91
65	3,485	-172	-4.703	+100.00

to the loss of elasticity in the walls of the alveoli. With these facts in mind, it is possible to predict that the tall youth will have the greatest vital capacity while the old man who is short of stature will have the least.

When body weight is averaged by years, no definite relationship between weight and age is apparent. If, however, the length of service in the fire department is related to age, a very definite correlation is obtained, the length of service increasing strikingly with advanced age.

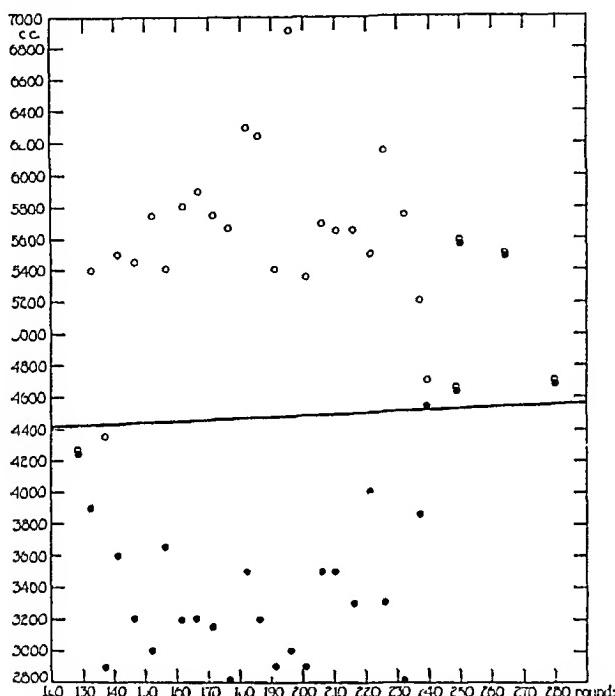


Fig 8.—Relation between maximum and minimum capacity values and body weight.

The range of variability as shown by the maximum and minimum values (Table 7 and Chart 6) shows wide variation. This variability ranges from about two fifths to one tenth of the calculated values on both sides of the central tendency curve.

The absolute and percentage deviations of the calculated from the observed averages are listed in Table 8. In only two instances were the percentage deviants more than 10 per cent, one average representing three cases and the other two.

The weighted average deviants of the vital capacity-age formula are given in Table 16. The weighted average absolute deviant is 116.2 cc and the weighted average percentage deviant, 2.69 per cent. The empiric formula, therefore, is practically as accurate as it was for body length and for stem length.

The percentage increment for five year periods grows steadily greater as the age increases (Table 9). The percentage increment is about 3.4 per cent between 20 and 25 years and becomes 4.7 per cent between 60 and 65 years.

A third of the total decrease in vital capacity during the age intervals of 20 to 65 years occurs by 35 years and two-thirds by 50 years.

Vital Capacity in Relation to Body Weight—Vital capacity is practically unaffected by an increase of body weight (Table 10 and Chart 7). There is a very slight rise in vital capacity with increasing weight, although the increase is so small that it falls within the margin of error. The vital capacity-body weight relationship can be expressed by the formula:

$$\text{Vital capacity (cubic centimeters)} = 0.46 \text{ times body weight (pounds)} + 4,350$$

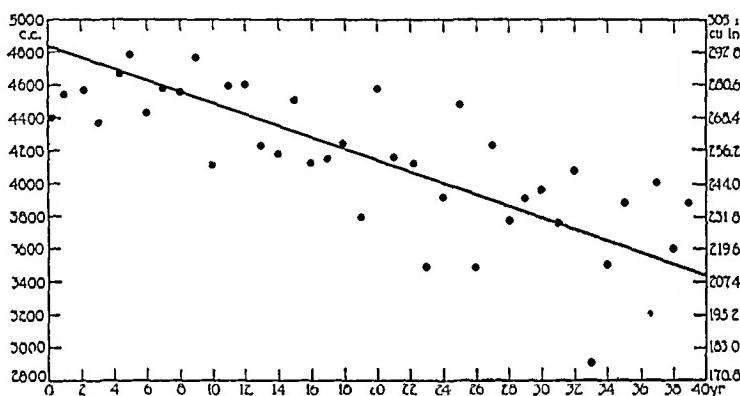


Fig. 9.—Relation between average vital capacity decrease and length of service in the fire department.

The absolute vital capacity increases steadily but very slightly from 4,405 cc at 120 pounds (54.4 kg) of body weight to 4,479 cc at 280 pounds (127 kg)—a total increase of 74 cc and an absolute increase of only 4.6 cc for every 10 pounds (4.5 kg) of body weight.

As the body weight becomes heavier, the standing and sitting height becomes longer. The vital capacity, however, does not follow the advance in weight even though it is accompanied by an increase in the standing and sitting height. This is probably due to the fact that lung growth accompanies the growth of the body in length. Increase in body weight, however, above the age of 21, is brought about to a large degree by subcutaneous and visceral fat deposits. The lung receives none of this additional weight, and, consequently, the vital capacity remains practically the same even when the body weight increases.

There is no constant relationship between body weight and age in this small series of cases.

TABLE 10—*Observed Vital Capacity of 418 Firemen Ranging in Body Weight from 125 to 285 Pounds (567 to 129.3 kg.)*

Body Weight, Pounds	Num ber of Cases	Standing Height, Inches	Age, Years	Vital Capacity, Cc			Length of Service, Years		Sitting Height, Inches	
				Maxi- mum	Min- imum	Mean	No. of Cases	Mean	No. of Cases	Mean
125-130	129.0	1	67.0	4,250	4,250	4,250	1	12.0	1	33.8
130-135	132.7	6	67.6	3,82	5,400	3,900	4,258	16.0	6	33.8
135-140	137.3	9	67.5	42.7	4,350	2,900	3,767	16.4	8	34.3
140-145	141.6	10	67.9	35.9	5,500	3,600	4,450	11.1	9	34.8
145-150	146.6	21	68.3	36.1	5,450	3,200	4,268	10.5	19	34.7
150-155	152.1	32	68.6	34.7	5,750	3,000	4,365	10.8	23	35.1
155-160	156.5	28	68.9	34.4	5,400	3,650	4,504	8.9	25	35.2
160-165	161.8	31	69.1	34.1	5,800	3,200	4,603	8.7	29	35.4
165-170	166.5	30	69.5	37.0	5,000	3,200	4,573	10.4	27	35.2
170-175	171.8	47	69.3	38.8	5,750	3,150	4,415	13.1	41	35.5
175-180	177.0	24	69.4	42.0	5,650	2,800	4,306	13.4	21	35.6
180-185	182.2	24	69.7	34.7	6,300	3,500	4,548	9.7	19	35.5
185-190	186.3	21	69.8	35.6	6,250	3,200	4,807	12.0	18	35.9
190-195	191.4	32	69.2	40.4	5,400	2,900	4,245	13.8	24	35.7
195-200	196.1	18	71.0	34.6	6,950	3,050	4,485	9.2	15	36.2
200-205	201.3	16	69.3	41.5	5,350	2,900	4,169	14.5	13	35.6
205-210	206.4	11	69.8	37.5	5,700	3,500	4,341	10.6	9	36.4
210-215	210.9	11	71.2	42.0	5,650	3,500	4,450	14.2	10	37.0
215-220	216.8	14	70.3	35.6	5,650	3,300	4,543	11.8	12	36.5
220-225	221.7	9	71.2	37.8	5,500	4,000	4,672	16.1	5	36.9
225-230	226.0	9	71.3	41.9	6,150	3,300	4,194	15.1	9	36.4
230-235	232.6	5	69.3	36.2	5,750	2,800	4,440	11.0	4	36.8
235-240	237.3	3	70.8	44.3	5,200	3,850	4,417	15.3	3	36.9
240-245	240.0	2	72.1	36.5	4,700	4,525	4,613	11.0	2	35.8
245-250	249.0	1	71.0	44.0	4,650	4,650	4,650	24.0	1	37.0
250-255	250.0	1	73.0	34.0	5,600	5,600	5,600	12.5	1	37.0
255-260										
260-265	264.0	1	73.5	54.0	5,550	5,550	5,550	12.0	1	37.0
265-270										
270-275										
275-280										
280-285	280.0	1	73.5	29.0	4,700	4,700	4,700	9.0	1	39.0

TABLE 11—*Observed and Calculated Vital Capacity of 418 Firemen Ranging in Body Weight from 125 to 285 Pounds (567 to 129.3 kg.)*

Body Weight, Pounds	Range	Mean	Observed Mean Vital Capacity, Cc	Calculated Vital Capacity, Cc	Deviation of Calculated from Observed Values	
					Cubic Centimeters	Per Cent
125-130	129.0		4,250	4,409	+ 159	+ 3.74
130-135	132.7		4,258	4,411	+ 153	+ 3.59
135-140	137.3		3,767	4,413	+ 646	+17.15
140-145	141.6		4,450	4,415	- 35	- 0.79
145-150	146.6		4,268	4,417	+ 149	+ 3.49
150-155	152.1		4,365	4,420	+ 55	+ 1.26
155-160	156.5		4,504	4,492	- 82	- 1.82
160-165	161.8		4,608	4,424	- 179	- 3.89
165-170	166.5		4,578	4,427	- 146	- 3.19
170-175	171.8		4,415	4,429	+ 14	+ 0.32
175-180	177.0		4,306	4,481	+ 125	+ 2.90
180-185	182.0		4,548	4,434	- 114	- 2.51
185-190	186.3		4,807	4,436	- 371	- 7.72
190-195	191.4		4,245	4,438	+ 193	+ 4.55
195-200	196.1		4,485	4,440	- 45	- 1.00
200-205	201.3		4,169	4,443	+ 274	+ 6.57
205-210	206.4		4,341	4,445	+ 104	+ 2.40
210-215	210.9		4,450	4,447	- 3	- 0.07
215-220	216.8		4,543	4,450	- 93	- 2.05
220-225	221.7		4,672	4,452	- 220	- 4.71
225-230	226.0		4,194	4,454	+ 260	+ 6.20
230-235	232.6		4,440	4,457	+ 17	+ 0.38
235-240	237.3		4,417	4,459	+ 42	+ 0.95
240-245	240.0		4,613	4,460	- 153	- 3.32
245-250	249.0		4,650	4,464	- 186	- 4.00
250-255	250.0		5,600	4,465	- 1,135	-20.27
255-260						
260-265	264.0		5,550	4,471	- 79	- 1.42
265-270						
270-275						
275-280						
280-285	280.0		4,700	4,479	- 221	- 4.70

The range of variability as shown by the maximum and the minimum values (Table 10 and Chart 8) is very large, reaching about from one quarter to one half of the calculated values on each side of the central tendency curve.

The absolute and percentage deviations of the calculated from the observed averages are shown in Table 11. In only two of the averages are the percentage deviants more than 10 per cent, one average representing only one case and the other nine.

The weighted average deviants of the vital capacity-length of formula are recorded in Table 16. The weighted average absolute deviant is 1,403, and the weighted average percentage deviant, 3.19 per

TABLE 12—Changes in Calculated Vital Capacity of 418 Firemen Ranging in Body Weight from 120 to 280 Pounds (54.4 to 127 kg.)

Body Weight, Pounds	Calculated Vital Capacity, C c	Increment		Percentage of Total Increment
		Cubic Centimeters	Percentage	
120	4,403.2			
130	4,409.8	4.6	0.1044	6.25
140	4,414.4	4.6	0.1043	12.50
150	4,419.0	4.6	0.1042	18.75
160	4,423.6	4.6	0.1041	25.00
170	4,428.2	4.6	0.1040	31.25
180	4,432.8	4.6	0.1039	37.50
190	4,437.4	4.6	0.1038	43.75
200	4,442.0	4.6	0.1037	50.00
210	4,446.6	4.6	0.1036	56.25
220	4,451.2	4.6	0.1034	62.50
130	4,455.8	4.6	0.1033	68.75
240	4,460.4	4.6	0.1032	75.00
250	4,465.0	4.6	0.1031	81.25
260	4,469.6	4.6	0.1030	87.50
270	4,474.2	4.6	0.1029	93.75
280	4,478.8	4.6	0.1028	100.00

cent. This signifies that it is not possible to fit the formula of vital capacity-body weight quite as closely as in the case of body length, stem length or age. The relation is still within bounds of comparative accuracy, however, and the formula probably expresses a true though slight increase in vital capacity when it is related to body weight.

The percentage increment (Table 12) decreases almost imperceptibly because the absolute increment of body weight is only 4.6 cc per 10 pounds (4.5 kg.).

Twenty-five per cent of the total increase in vital capacity between 120 and 280 pounds (54.4 and 127 kg.) of body weight has occurred at a body weight of 160 pounds (72.6 kg.), 50 per cent at a weight of 200 pounds (90.7 kg.), and 75 per cent at 240 pounds (108.8 kg.).

Vital Capacity in Relation to the Length of Service in the Fire Department—Vital capacity steadily declines as the length of the service increases (Table 13 and Chart 9). The decrease in vital capacity in terms of years of service may be expressed by the empiric formula

Vital capacity (cubic centimeters) = 4,840 — 34.84 times length of service (years)

The absolute vital capacity decreases steadily from 4,840 c.c. at the entrance to the fire department to 3,446 c.c. at the close of forty years of service, a decline of 174 c.c. every five years (Table 15)

TABLE 13—*Observed Vital Capacity of 345 Firemen Ranging in Length of Service up to Forty Years*

Length of Service, Years		Number of Cases	Standing Height, Inches	Sitting Height, Inches	Age, Years	Body Weight, Pounds	Vital Capacity, Cc		
Range	Mean						Maximum	Minimum	Mean
0-1	0.3	1	71.8	35.5	22.0	150.0	4,400	4,400	4,400
1-2	1.0	10	69.9	35.9	32.9	175.1	6,000	3,500	4,538
2-3	2.2	5	69.4	34.7	32.0	174.8	5,750	4,100	4,560
3-4	3.1	4	68.5	35.3	30.5	154.0	5,000	3,650	4,362
4-5	4.4	70	69.1	35.6	29.1	173.7	6,950	3,200	4,662
5-6	5.0	46	69.7	35.7	29.5	175.4	6,200	3,200	4,778
6-7	6.0	6	70.2	36.0	31.0	184.5	5,200	3,050	4,425
7-8	7.0	8	69.8	35.7	31.6	159.4	5,700	3,200	4,575
8-9	8.0	11	69.9	35.6	31.5	179.2	5,500	4,050	4,564
9-10	9.0	17	70.4	35.8	32.2	188.2	5,800	3,600	4,762
10-11	10.0	9	68.6	35.1	38.3	176.9	5,200	3,250	4,106
11-12	11.0	13	69.7	36.3	36.9	187.2	6,150	3,750	4,592
12-13	12.1	16	69.1	35.1	37.6	182.8	5,600	3,300	4,602
13-14	13.0	11	70.0	35.9	41.5	177.5	5,400	2,900	4,223
14-15	14.0	13	68.6	35.1	41.6	171.4	5,200	3,000	4,173
15-16	15.0	7	70.2	35.9	42.9	189.1	5,400	3,700	4,500
16-17	16.0	8	69.8	36.2	45.3	194.0	5,100	2,900	4,119
17-18	17.0	7	69.1	35.3	48.0	167.8	5,650	3,200	4,143
18-19	18.1	8	69.2	35.4	44.5	182.5	5,300	3,150	4,238
19-20	19.1	9	68.4	35.1	49.7	170.5	4,450	3,200	3,789
20-21	20.0	9	70.8	36.0	48.2	193.6	5,550	3,400	4,567
21-22	21.0	4	68.7	35.8	46.2	185.5	4,600	3,650	4,150
22-23	22.2	7	70.4	35.7	51.9	183.0	4,800	3,600	4,119
23-24	23.0	3	68.1	35.3	49.0	183.0	3,800	3,150	3,483
24-25	24.0	4	68.9	35.5	56.0	199.8	4,650	2,900	3,912
25-26	25.0	1	67.5	32.0	55.0	149.0	4,475	4,475	4,475
26-27	26.0	2	68.4	35.1	50.5	207.5	3,650	3,300	3,475
27-28	27.0	4	69.1	35.8	57.0	179.0	4,400	4,050	4,225
28-29	28.0	6	68.7	35.1	57.0	185.5	4,400	3,500	3,767
29-30	29.0	6	69.5	35.6	53.0	167.3	4,900	3,250	3,900
30-31	30.0	6	68.8	34.5	55.7	184.8	4,800	2,800	3,958
31-32	31.0	4	69.9	35.2	59.3	181.0	5,000	2,900	3,750
32-33	32.0	2	68.2	35.4	55.5	170.5	4,250	3,900	4,075
33-34	33.0	1	67.3	36.0	59.0	177.0	2,900	2,900	2,900
34-35	34.0	1	63.3	33.5	61.0	189.0	3,500	3,500	3,500
35-36	35.0	2	67.4	34.8	57.5	173.0	3,900	3,850	3,875
36-37	37.0	1	64.5	33.0	61.0	133.0	4,000	4,000	4,000
38-39	38.0	1	70.7	33.8	63.0	186.0	3,600	3,600	3,600
39-40	39.0	2	71.5	35.4	62.5	191.0	4,150	3,600	3,875

As the length of service increases, so also does the age. In fact, the decline in vital capacity is undoubtedly due to the advancing age rather than to the length of service.

The body weight, body length and stem length remain practically the same throughout the entire length of service.

The range of variability, as shown by the maximum and the minimum values (Table 13 and Chart 10) varies between one third and one fourth of the calculated values on each side of the curve of central tendency.

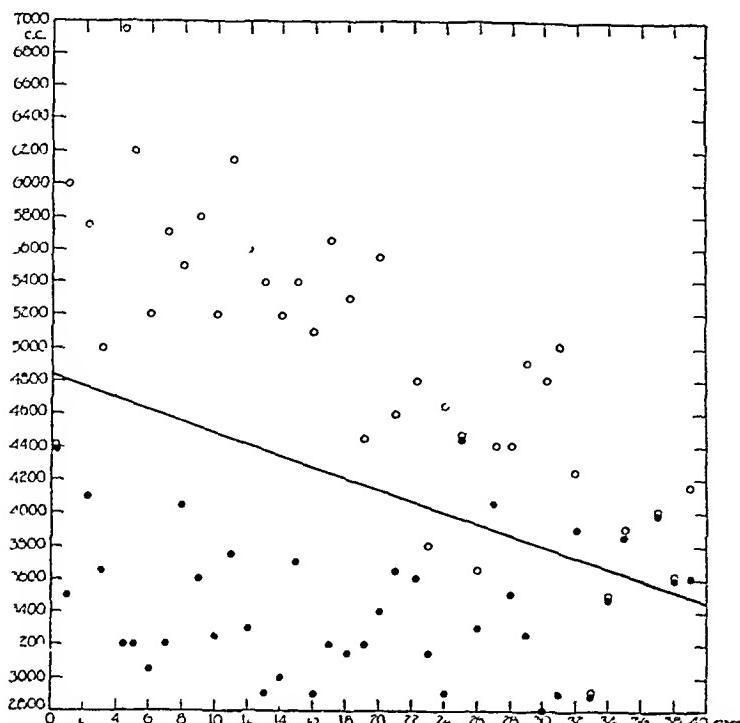


Fig. 10.—Relation between maximum and minimum vital capacity values and length of service in the fire department

TABLE 14.—*Observed and Calculated Vital Capacity of 345 Firemen Ranging in Length of Service up to Forty Years*

Length of Service, Years		Observed Mean Vital Capacity, C.c.	Calculated Vital Capacity, C.c.	Deviation of Observed from Calculated Values	
Range	Mean			Cubic Centimeters	Per Cent
0- 1	0.3	4,400	4,830	+430	+ 9.77
1- 2	1.0	4,538	4,805	+267	+ 5.88
2- 3	2.2	4,660	4,763	+203	+ 4.45
3- 4	3.1	4,302	4,732	+370	+ 8.48
4- 5	4.4	4,662	4,687	+25	+ 0.54
5- 6	5.0	4,778	4,666	-112	- 2.34
6- 7	6.0	4,425	4,631	+206	+ 4.66
7- 8	7.0	4,515	4,506	+21	+ 0.46
8- 9	8.0	4,564	4,561	-3	- 0.07
9-10	9.0	4,762	4,526	-2%6	- 4.96
10-11	10.0	4,106	4,492	-286	+ 9.40
11-12	11.0	4,592	4,457	-135	- 2.94
12-13	12.1	4,602	4,418	-184	- 3.98
13-14	13.0	4,223	4,387	+164	+ 3.88
14-15	14.0	4,173	4,352	-179	+ 4.29
15-16	15.0	4,500	4,317	-183	- 4.07
16-17	16.0	4,119	4,283	-164	+ 3.98
17-18	17.0	4,143	4,248	+105	+ 2.53
18-19	18.1	4,238	4,209	-29	- 0.18
19-20	19.1	3,789	4,175	+286	+10.9
20-21	20.0	4,507	4,143	-424	- 9.28
21-22	21.0	4,150	4,108	-42	- 1.01
22-23	22.2	4,119	4,067	-52	- 1.36
23-24	23.0	3,483	4,099	+516	-15.96
24-25	24.0	3,912	4,004	+92	+ 2.35
25-26	25.0	4,475	3,969	-1106	-11.21
26-27	26.0	3,475	3,935	+460	-13.24
27-28	27.0	4,225	3,899	-26	- 7.72
28-29	28.0	3,767	3,864	+91	+ 2.58
29-30	29.0	3,900	3,820	-70	- 1.79
30-31	30.0	3,958	3,795	-163	- 4.12
31-32	31.0	3,750	3,760	+10	+ 0.27
32-33	32.0	4,075	3,725	-250	- 8.50
33-34	33.0	2,900	3,690	+790	+27.24
34-35	34.0	3,500	3,655	+155	+ 4.42
35-36	35.0	3,875	3,621	-254	- 6.55
36-37					
37-38	37.0	4,000	3,551	-449	-11.22
38-39	38.0	3,600	3,516	-84	- 2.22
39-40	39.0	3,575	3,481	-394	-10.17

The absolute and percentage deviations of the calculated from the observed values (Table 14) are quite evenly distributed. In seven of the average points, however, the percentage deviation is more than 10 per cent. Three of these averages represent only one case, two of them stand for only two cases, one for three, and one for nine.

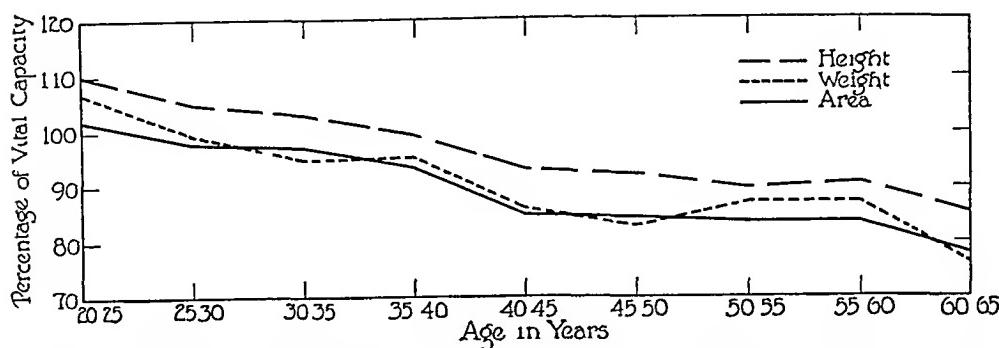


Fig. 11.—Vital capacity percentages obtained from formulas of Dreyer, West and others plotted against age.

The weighted average deviants of the vital capacity-length of service formula (Table 16) are larger than the deviants of the other vital capacity formulas already described. The weighted average absolute deviant is 150.2 and the weighted average percentage deviant, 3.52.

TABLE 15—Changes in Calculated Vital Capacity of 345 Firemen Rauging in Length of Service up to Forty Years

Length of Service, Years	Calculated Vital Capacity, Cc	Decrement		Percentage of Total Decrease
		Cubic Centimeters	Percentage	
0	4,840			
5	4,666	-174	-3.595	12.48
10	4,492	-174	-3.729	24.96
15	4,317	-175	-3.896	37.52
20	4,143	-174	-4.031	50.00
25	3,969	-174	-4.200	62.48
30	3,795	-174	-4.384	74.96
35	3,621	-174	-4.585	87.45
40	3,446	-175	-4.833	100.00

TABLE 16—Formulas of Vital Capacity with the Average Weighted Deviants (Y, Vital Capacity in Cubic Centimeters)

X	Formulas	Average Weighted Deviants	
		Absolute Cc	Per Cent
Standing height, inches	$Y = 159.9X - 6,655$	104.1	2.33
Sitting height, inches	$Y = 218.9X - 3,299$	112.8	2.53
Body weight, pounds	$Y = 0.46X + 4,350$	140.3	3.19
Age, years	$Y = 5,725 - 34.46X$	116.2	2.69
Length of service in fire department, years	$Y = 4,840 - 34.84X$	150.2	3.52

The percentage increment for five year intervals of service increases rather rapidly. Between 0 and 5 years, the increment is about 36 per cent, and, between 35 and 40, it becomes about 48 per cent.

Twenty-five per cent of the total decrease in vital capacity during the thirty-nine years of service in the fire department is accomplished by the tenth year of service, 50 per cent by the twentieth year and 75 per cent by the thirtieth year.

After this study was made, it was decided to apply some normal standards already in use to our data. The standards used were the surface area standard of West, the standing height standard of West and the formula of Dreyer $\frac{Wt^{0.72}}{VC} = 0.69$. Figure 11 shows that the curves prepared on the basis of surface area and Dreyer's formula very nearly coincide. This is in accordance with the findings of West, Myers and Cady and others. Indeed, it is to be expected since, in the formula of Dreyer, the surface area was duly considered. The curve prepared from the standing height standard shows that slightly higher percentages were obtained for the entire group when this standard was used. It is interesting to note that the Minneapolis firemen presented vital capacities well within normal limits by the surface area and Dreyer's formula until the age of 40 to 45 years was reached. After that age, they remained only slightly below normal limits until the age of 60 to 65 years was reached, when they dropped below 80 per cent of the normal. When the standing height standard was employed, the average vital capacity was practically within normal limits until the age of 60 to 65 years.

PANCREATIC ENZYMES IN CHOLECYSTITIS *

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Cholecystitis is frequently associated with a certain degree of pancreatitis. Of 1,290 cases of diseases of the gallbladder and bile duct reported by Judd,¹ 347 or 26.8 per cent had associated pancreatitis. In his cases, the clinical history did not, as a rule, suggest pancreatitis. The condition was determined at the time of operation by enlargement, hardening or edema of the pancreas. Deaver believes that cholecystitis causes a pancreatic lymphangitis, which condition precedes interstitial pancreatitis. Pancreatitis is sufficiently far advanced in over one fourth of the cases of gallbladder disease operated on to cause a macroscopic change in the organ. Another interesting illustration of the intimate relationship between gallbladder and pancreatic disease is the not infrequent occurrence of glycosuria in long standing cholecystitis.

In routine examination of the fasting duodenal juice for pancreatic enzymes, we frequently encountered an absence of, or a decrease in, the amount of one or more enzymes in cases of cholecystitis. It was decided to study the external secretion of the pancreas in a series of cases of proved cholecystitis, in order to ascertain whether the pancreatic involvement in cholecystitis is sufficient to cause a consistent reduction in the amount of enzyme present. The direct examination of the duodenal juice for pancreatic enzymes was first reported by Einhorn,² in 1910, following his discovery of the duodenal bucket, in January of the same year. This discovery opened up an entirely new field for investigation. It would seem that when pancreatic juice can be obtained directly for examination, a test based on such an examination should be the most reliable method available. The suprarenal mydriasis test of the Loewi, the iodobehenic test of Winternitz, the urinary diastase test and the Sahli capsule all have their advocates and all yield information of value to those familiar with their significance, but none of them alone is an absolute measure of pancreatic function.

* From the gastro-intestinal clinic of the Graduate School of Medicine of the University of Pennsylvania

1 Judd, E S The Relation of the Liver and the Pancreas to Infection of the Gallbladder, J A M A **77** 197 (July 16) 1921

2 Einhorn, Max Experiences with Duodenal Contents, J A M A **55**, July 2, 1910

METHOD

Einhorn³ has devised an ingenious method of testing for pancreatic enzymes. It is patterned somewhat after the Mett tube method for pepsin determination, except that agar is used as a vehicle. The principle is that agar tubes in which albumin, starch and fat are mixed allow the ferment action to take place in them by osmosis. If the test substances are colored with indicators that undergo a change when acted on, it is easy to ascertain the presence of the ferments, and also to estimate their approximate amount by the volume of the tube change recorded in millimeters. When this study was first undertaken, several of the more complicated chemical methods were scrutinized and tried, but the method of Einhorn⁴ was finally selected. It is undoubtedly the simplest method that can be considered at all reliable, and at the same time yields information as to the amount of enzyme present.

There is still a great deal to be desired so far as a method for accurately determining the amount of ferment is concerned. The basic principles of the chemistry of enzyme action are probably more nearly conformed to in the method recently described by McClure, Wetmore and Reynolds⁵. This method is too involved for routine clinical work and will probably never be universally adopted. The method selected is not alone responsible for the varied and conflicting results obtained. A frequent source of error is in the manner of collecting the duodenal juice for examination. There are extrapancreatic enzymatic substances selected for testing. Withdrawing chyme saturated with gastric juice from the duodenum, and subjecting it to examination for pancreatic enzymes, we believe to be a frequent source of confusion.

The fractional pancreatic analysis, as described by Einhorn, was done on eleven patients (Table 8). We feel that the information derived from the fractional method does not justify the additional two hours necessary to perform the test. It is possible to obtain the fasting duodenal juice, utilize it for pancreatic enzyme determination, and proceed with a Lyon-Meltzer bile drainage at one tubing. We agree with Friedenwald and Einhorn, that the fasting duodenal juice represents the highest point of enzyme concentration. At least, it represents the highest concentration level which can be obtained from a duodenum free from food and gastric juice. After a meal there is a drop in enzyme values, which gradually rise until the fasting figure is reached in about two hours. There is considerable fluctuation normally.

3 Einhorn, Max M Rec, Jan 15, 1910

4 Einhorn, Max The Duodenal Tube, Philadelphia, W B Saunders Company, 1921

5 McClure, C W, Wetmore, A S, and Reynolds, L New Methods for Estimating Enzymatic Activities of the Duodenal Contents of Normal Man, Arch Int Med 27 706 (June) 1921

Another factor which militates against the fractional method is that chyme is dumped into the duodenum at intervals, and it is impossible to tell what proportion of digestion is due to gastric juice and what amount is due to pancreatic enzymes.

METHOD OF OBTAINING SECRETION

The patient reports in the morning on a fasting stomach. The stomach is washed until clean and aspirated until dry, with the patient in the recumbent position. The tube is allowed to pass into the duodenum, the technic of Lyon being used. If there is free fluid in the duodenum, it is gently aspirated. If not, the tube is attached to a

TABLE 1—*Normal Gall Tract*

No	Age	Date	Diagnosis	Amylopsin	Trypsin	Stearnsin
1	66	12/18/22	Normal	7	3	6
2	39	12/18/22	Normal	4.5	1.5	10.5
3	39	12/ 8/22	Normal	7	3	4
4	46	12/ 8/22	Normal	10.5	8.5	3.5
5	29	12/18/22	Normal	5	3	1
6	46	12/ 8/22	Normal	7	9.5	5.5
7	40	12/14/23	Achylia gastrica, indolic putrefaction	6.5	2.8	2.5
8	27	1/ 4/24	Spinal arthritis	4	9	10
9	39	8/16/22	Normal	20	3	2
10	33	2/13/24	Duodenal ulcer	5	3	1
11	37	2/16/24	Normal	0	7	5
		2/26/24		3.5	4.5	5
12	39	3/15/24	Achylia, syphilis	8.5	2	0.5
13	44	3/15/24	Duodenal ulcer	5	2	0.5
14	28	3/15/24	Gastric ulcer	6	1.5	1.5
15	39	3/19/24	Duodenal ulcer	6	0.5	0.5
16	16	3/19/24	Chronic appendicitis	0	0.5	0
17	44	3/25/24	Normal	9	2	0.5
		2/ 9/24		4	2	2
18	33	3/25/24	Normal	8.5	7	1
19	42	4/12/24	Achylia gastrica	11	8	10
		3/25/24		11	0	1.5
20	40	4/ 5/24	Stiller's disease	15	5	1
21	27	3/29/24	Normal	8	6	1.5
22	24	3/29/24	Catarrhal gastritis	10	4	1
23	60	3/29/24	Pyloric ulcer	8	2	5
24	31		Normal	14	10	20
25	30	4/ 1/24	Duodenal ulcer	10	20	5
26		4/12/24	Normal	20	8	11
Group average				8.3	5	3.5

bottle until about 10 cc of duodenal juice has been drained out. It is placed in a test tube and 1 drop of toluene is added to stop any bacterial activity. The Einhorn agar tubes, one each of starch, hemoglobin and olive oil, are dropped into the test tube after the end of the Einhorn tube covered with paraffin has been filed off. The test tube is placed in an incubator for twenty-four hours. Then it is removed, and the amount of digestion in each tube is measured in millimeters. The tubes must be freshly prepared each month and kept in the icebox. A tube in which the agar does not adhere to the capillary glass tube all the way down or one that has started to dry out should be discarded.

In Table 1 are grouped twenty-six patients whose gall tracts were normal. They were thoroughly studied from a gastro-intestinal stand-

point. The history, physical examination and the Meltzer-Lyon bile drainage yielded negative results in every case. A large proportion of them had negative roentgen-ray and fluoroscopic studies. Amylopsin varied from 0 to 20 mm., seven patients had amylopsin reading of over 10 mm., two patients had a reading of zero for the starch enzyme, but one of them at another time had 3.5 mm. for amylopsin. The other patient was a vagotonic boy who had chronic appendicitis. It is probable that the irritation of the tube set up a sympathetic vagus reflex, which caused a temporary suppression of pancreatic juice. In this case there was a complete absence of amylopsin and steapsin, and only 1.5 mm. of digestion in the hemoglobin tube. The average amount of amylopsin found in the fasting duodenal residuum in this series of normal gall tract cases was 8.3 mm.

Friedenwald and Sindler⁶ report a variation of from 1 to 15 mm. in amylopsin, in a series of normal cases. Their average amount of amylopsin, in normal cases, was 2.29 mm. Einhorn states that 6 mm. is the average amount of amylopsin found in normal cases. It is obvious that the starch enzyme is subject to very wide fluctuations, even in normal cases. Needless to say, a considerable source of error will be avoided if the same individual is assigned to make the readings. Amylopsin is the most variable of the pancreatic enzymes and the least reliable in computing pancreatic function.

Trypsin readings, in the normal group, varied from 0.5 to 20 mm. In only one case was more than 10 mm. of digestion found (the smaller range of fluctuation as compared with amylopsin should be noted), 5 mm. was the average amount of trypsin for this group. Friedenwald and Sindler's variation was from 1 to 12 mm., and their average for this enzyme was 5.8 mm., Einhorn's normal average was 2.8 mm. The range of fluctuation is not nearly so great as with amylopsin, but it is still considerable.

The amount of steapsin in the normal group varied from 0 to 20 mm., but only three cases had a reading of over 10 mm. The average amount of steapsin present was 3.5 mm. Friedenwald and Sindler give from 1 to 12 mm. as their normal range of fluctuation, and 3.5 mm. as the average amount found. Einhorn's average for steapsin was 3.5 mm. Steapsin is the least variable of the enzymes and is probably the most important in the study of pancreatic dysfunction. It can be seen at a glance by consulting the first table that the strength of one enzyme is independent of the strength of the others. Friedenwald, Sindler and Einhorn are of the same opinion.

⁶ Friedenwald, J., and Sindler, J. Fractional Analysis of the Duodenal Contents in Normal Individuals, *J. A. M. A.* **177**, 1469 (Nov 5) 1921.

In recording the degree of fluctuation of enzymes, when more than one examination was made on a patient, the extreme figures were used. In computing the average amount of enzyme present in each series, if two or more examinations were made on one patient, the average amount

TABLE 2.—*Gallbladder Disease*

No	Age	Date	Diagnosis	Duration of Symptoms			
				Years	Amylase sin	Trypsin sin	Steap sin
1	60		Chronic cholecystitis	15	25	2	1
2	46	8/12/22	Chronic cholecystitis	10	7	3	4
		8/11/24			7	1	1
3	36	8/19/22	Subacute cholecystitis	2	2	2	
4	35	8/15/22	Subacute cholecystitis	2	14	15	3
5	39	8/22/22	Cholelithiasis, operation	15	2	0	
6	29	8/15/22	Chronic cholecystitis	1	7	7	3
7	36	2/11/24	Chronic cholecystitis, operation	9	2	1	7
8	28	12/ 4/23	Chronic cholecystitis	5	2	15	125
		12/ 7/23			5	3	0
9	44	12/ 8/23	Chronic cholecystitis, operation	8	0	15	1
10	41	12/ 8/23	Cholelithiasis, operation	5	5	6	65
11	43	12/18/23	Chronic cholecystitis	10	4	1	1
12	49	12/18/23	Cholelithiasis, operation	11	15	1	1
13	29	12/11/23	Chronic cholecystitis, duodenal ulcer	4	2	1	1
14	34		Giardiasis, cholecystitis	10	5	5	3
15	25	1/ 8/24	Ankylostomiasis, chronic cholecystitis	3	85	2	0
16	24	1/15/24	Chronic cholecystitis, chronic appendicitis	2	0	5	1
17	30	2/ 5/24	Chronic cholecystitis	3	2	1	0
18	26	2/ 9/24	Giardiasis, chronic cholecystitis	3	3	0	4
		2/15/24			6	2	4
		3/11/24			2	1	7
19	74		Chronic cholecystitis	30	0	1	5
20	43	2/ 9/24	Chronic cholecystitis, mucouscolitis	5	0	5	0
21	41		Cholelithiasis, operation	10	15	1	1
22	33	2/ 9/24	Chronic cholecystitis	10	0	15	05
23	39	2/23/24	Chronic cholecystitis	7	7	1	05
24	40	2/26/24	Chronic cholecystitis	3	0	1	0
25	30	2/26/24	Chronic cholecystitis	2	0	1	0
		2/16/24			0	5	0
		3/15/24			2	2	0
26	48	2/26/24	Cholelithiasis	10	0	1	0
27	48	3/ 1/24	Cholelithiasis, operation	10	2	0	0
28	23	2/ 5/24	Chronic cholecystitis, chronic appendicitis	Under 2	9	12	2
		2/19/24			9	05	1
29	32	2/ 5/24	Chronic cholecystitis	4	0	05	0
		3/ 5/24			7	6	0
		3/29/24			8	1	1
30	32	2/ 5/24	Chronic cholecystitis	Over 5	1	1	0
31	42	2/ 5/24	Chronic cholecystitis		0	2	1
		3/11/24			3	15	1
32	44	2/ 5/24	Chronic cholecystitis, operation	10	5	25	3
		3/ 5/24			8	3	15
		3/11/24			0	05	0
33	36	3/19/24	Chronic cholecystitis, syphilis	6	10	15	1
34	25	3/20/24	Chronic cholecystitis	3	3	1	0
35	21		Chronic cholecystitis	1	0	05	0
36	50	4/ 5/24	Chronic cholecystitis	20	7	1	5
37	46	3/21/24	Cholelithiasis	10	4	1	5
38	38	4/12/24	Cholelithiasis, operation	13	8	4	5
39	54	10/12/23	Chronic cholecystitis	10	0	0	0
		12/ 4/23			0	0	0
		4/ 5/24			0	0	0
40	57		Chronic cholecystitis	5	5	2	2
Group average					30	21	16

for each enzyme was computed and the resultant figure was used for that patient's normal, rather than the extreme figures. The most disappointing part of the normal group is the wide degree of fluctuation which occurs in the same patient when the pancreatic function is tested more than once under exactly the same conditions.

In Case 10, two examinations were made, ten days apart. There was a difference of 35 mm of amylase and 25 mm of trypsin, but the steapsin readings were identical. Two determinations were made on Case 17, six weeks apart. The difference in amylase was 5 mm, in trypsin 15 mm, and in steapsin 15 mm. Two determinations were made on Case 19, three weeks apart. Amylase was the same, but a difference of 8 mm was present in the two readings for trypsin, and a discrepancy of 85 mm in the steapsin readings. This emphasizes again the great variability even in the same individual and under like conditions. In a doubtful case, more than one determination should be done and a careful feces analysis made. Whipple⁷ studied a series

TABLE 3—Variation in Quantity of Enzyme

	Extremes in Amount of Amylase	Extremes in Amount of Trypsin	Extremes in Amount of Steapsin
Gall tract normal group, Table 1	0 to 20 7 cases over 10	0 to 20 1 case over 10	0 to 20 2 cases over 10
Gallbladder disease group, Table 2	0 to 11 1 case over 10	0 to 12 1 case over 10	0 to 7

TABLE 4—Relation Between Duration of Symptoms and Amount of Enzyme Present in Cholecystitis

Duration of Symptoms	Average Amount of Amylase	Average Amount of Trypsin	Average Amount of Steapsin	Number of Cases
Ten years or more	3.2	1.5	1.8	16
From 5 to 9 years	3.3	2.1	1.8	11
From 2 to 4 years	2.9	1.8	1.1	11
Under 2 years	5.3	4.5	1.5	3

of cases for pancreatic ferments before operation and concluded that the interpretation of decreased activity in any one or more of three enzymes is difficult, and suggests checking any questionable case with a stool examination. He believes that gross changes at operation are not necessarily an indication of functional disturbance of the pancreas.

GALLBLADDER DISEASE

Forty cases of gallbladder disease were studied in the manner outlined above. The diagnosis was confirmed by operation in nine cases. The roentgen-ray studies indicated a pathologic gallbladder in nine other cases. In the remaining twenty-two cases, the diagnosis was made by the usual diagnostic procedures, history, physical examination and the Lyon-Meltzer drainage method. These cases will be found in Table 2. There was a variation in the starch enzyme in this group.

⁷ Whipple, A. O.: Use of the Duodenal Tube in Preoperative Study of the Bacteriology and Pathology of the Biliary Tract and Pancreas, Ann Surg 73: 556 (May) 1921.

of from 0 to 14 mm. In only one case was the reading over 10 mm. The proteolytic enzyme varied from 0 to 12 mm, with only one reading over 10 mm. Steapsin varied from 0 to 7 mm. By consulting Table 3, it will be seen that the range of fluctuation is distinctly less in the cholecystitis cases. This is more noticeable in the fat splitting enzyme, which did not rise above 7 mm. This marked reduction in the amount of fat splitting enzyme in cholecystitis may be more of a factor in the causation of poor fat digestion than is generally believed. The incomplete handling of fats in cholecystitis has usually been considered to be caused by a disturbance of the mechanism at the ampulla of Vater resulting in an insufficient quantity of bile being poured out into the intestines during the digestive phase.

TABLE 5—*Chololithiasis*

No.	Age	Date	Diagnosis	Duration of Symptoms,			
				Years	Amylopsin	Trypsin	Steapsin
1	39	8/22/22	Operation	15	2	2	
2	41	12/8/23	Operation	5	5	6	6.5
3	49	12/18/23	Operation	11	1.5	1	1
4	41		Operation	10	1.5	1	1
5	48	2/26/24		10	0	1	0
6	48	3/1/24	Operation	10	2	0	0
7	38	4/12/24	Operation	13	8	4	5
8	46	3/21/24		10	4	1	5
Group average					3	2	2.6

TABLE 6—*Disease of the Pancreas and Liver, Not Cholecystitis*

No.	Age	Date	Diagnosis	Amylopsin	Tryp-	Steap-
1	31	1/29/24	Diabetes	0	0	0
2		1/21/24	Diabetes	5	1	1.5
3	26	1/29/24	Arshenamin jaundice	9.5	2	3
4	30	2/19/24	Arshenamin jaundice	3.5	1	2
5	29	2/26/24	Arshenamin jaundice	5.5	4.5	3
6	46	1/8/24	Intestinal cancer metastasis to liver	0	1.5	4
7	46	2/19/24	Myocarditis cirrhosis of liver, etc.	2	2	3

A further study of Table 2 reveals a persistent absence of all enzymes in one case, and a persistent absence of two enzymes in three cases. Trypsin was absent from the fasting duodenal juice in three instances. Amylopsin was absent in eleven cases and steapsin in ten cases. In the cholecystitis cases in which the enzymes are considerably below normal, there is less fluctuation in the amount of enzyme from day to day. The fat splitting enzyme varies less when more than one determination is made on one patient.

The average amount of amylopsin present in the series of forty cases of gallbladder disease was 3.6 mm, as compared with 8.3 mm in the normal group (Table 7). The average amount of trypsin was 2.1 mm, as compared with 5.0 in the normal group. The group average for steapsin was 1.8 mm, as compared with 3.5 mm in the normal group.

Of the series of forty cases of cholecystitis, seventeen cases, or 42.5 per cent, had all three enzymes reduced in amount more than 50 per cent, eleven cases, or 27.5 per cent, had a reduction of over 50 per cent in two enzymes, and six cases, or 15 per cent, had a reduction of over 50 per cent in one enzyme. Eighty-five per cent of the cases studied having a gallbladder pathologic condition had a reduction of over 50 per cent in one or more enzymes. In making this computation, when more than one determination was made on the same individual, the highest reading was used and not the average reading for that patient.

Dowden and Enfield,⁸ using the method described by Whipple, concluded that the pancreatic enzyme determination was too variable to be reliable. The method used was not a quantitative one. An analysis of their cases shows that of twenty-seven cases of gall tract disease, 25 per cent had a complete absence of trypsin, and 14 per cent had no steapsin, whereas in twenty-five cases in which there was no gall

TABLE 7.—*Group Averages*

Diagnosis	Number of Cases	Amylopsin	Trypsin	Steapsin
Gall tract normal, Table 1	26	8.3	5	3.5
Gallbladder disease, Table 2	40	3.6	2.1	1.6
Cholelithiasis, Table 5	8	3	2	2.6
Diabetes, Table 6	2	2.5	0.5	0.7
Arsphenamin jaundice, Table 6	3	5.8	2.5	2.7

tract pathologic conditions, amylopsin was absent in five cases, trypsin in one, and steapsin in six cases.

In order to determine what relation existed between duration of disease and degree of reduction of enzymes, the cases of cholecystitis were subdivided into four groups (Table 4). In the few cases in which the duration of symptoms was under two years, the amount of enzyme present was practically the same as the average for the normal group. There seemed to be little difference, however, between the amount of enzyme present in the patients having symptoms between two and four years and those having symptoms over ten years.

CHOLELITHIASIS

Eight of the patients included in Table 2 had gallstones. They have been classified separately in Table 5 to ascertain if there was a greater reduction in the stone cases. The average amounts of amylopsin (3 mm.) and trypsin (2 mm.) are slightly below the amounts of those enzymes in the general cholecystitis group. The steapsin average is slightly above that of the cholecystitis group (Table 7). Although the

⁸ Dowden, C. W., and Enfield, C. D. The Duodenal Tube in the Study of Liver and Pancreatic Pathology, *South. M. J.* **15** 103 (Feb.) 1922.

number of cases is too small to base conclusions, there seems to be little difference between cholelithiasis and cholecystitis in their effect on the external secretion of the pancreas.

Two cases of diabetes were studied (Table 6). All three enzymes were absent in one case, and in the other there was a marked reduction in the amount of trypsin and steapsin.

Three cases of arsphenamin jaundice show an average slight reduction in all three enzymes.

TABLE 8.—*Fractional Pancreatic Analysis*

Case	Enzymes	Fasting	½ Hour	1 Hour	1½ Hours	2 Hours
			after Food	after Food	after Food	after Food
1 Gall tract normal	Amylopsin	0	5	9	10	8
	Trypsin	2	1	4	3	5
	Steapsin	0.5	0.5	1.5	0.5	0.5
2 Chronic cholecystitis	Amylopsin	7	2	7	0.5	4
	Trypsin	1	4	2.5	1	1
	Steapsin	1	1	1	0	1
3 Chronic cholecystitis	Amylopsin	2.5	3	3	3	4.5
	Trypsin	2	0.5	2.5	1.5	2
	Steapsin	1	0.5	1.5	1	0.2
4 Chronic cholecystitis	Amylopsin	2	2	0	1.5	2
	Trypsin	2	1	0	0.5	1
	Steapsin					
5 Chronic cholecystitis	Amylopsin	5	3	4	5	5
	Trypsin	1	1.5	3	2	2
	Steapsin	4	0.5	0.5	4	4
6 Chronic cholecystitis	Amylopsin	3	4	2.5	6	6
	Trypsin	1.5	2	3	3	2
	Steapsin	1	1	0	1.5	2
7 Chronic cholecystitis	Amylopsin	5	8	0	2	4
	Trypsin	2.5	3	0.5	1	1
	Steapsin	3	1.5	0	0.5	0.5
8 Chronic cholecystitis	Amylopsin	0	0	2	4	4
	Trypsin	0.5	0.5	0.5	0.5	0.5
	Steapsin	0	0	0	0.5	0.5
9 Chronic cholecystitis	Amylopsin	8	10	6	7	
	Trypsin	4	9	8	8	
	Steapsin	5	15	10	0	
10 Diabetes	Amylopsin	0	6.5	7	12.5	8
	Trypsin	0	1	3	2	2
	Steapsin	0	0	0	3.5	1
11 Normal	Amylopsin	2.5	4	6	3	3
	Trypsin	1	1.5	1.5	1	2.5
	Steapsin					

SUMMARY

1 A series of twenty-six cases having normal gall tracts were studied by the Einhorn agar tube method for pancreatic enzymes, using the fasting duodenal juice for the determination.

2 The fractional pancreatic analysis has a greater source of error and is more time consuming.

3 There is considerable range of variation in all of the enzymes, even in the same individual. Amylopsin is the most variable and the least stable. Trypsin and steapsin are almost on a par as to degree of variability, steapsin probably varying less. In patients having normal

gall tracts and without disease of the pancreas, we found the average amount of enzymes to be amylase, 83 mm., trypsin, 50 mm., and steapsin, 35 mm.

4 Forty cases of cholecystitis were studied in a similar manner. The range of fluctuation in the amount of enzyme was found to be greatly reduced in gallbladder disease. This was particularly true of steapsin.

5 A considerable number of cases of gall tract disease had one or more enzymes absent.

6 The average amount of each enzyme in cholecystitis was reduced to more than 50 per cent of the normal amounts.

7 Eighty-five per cent of all cases of gallbladder disease studied had a reduction of over 50 per cent in the amount of one or more of the enzymes.

8 The fat splitting enzyme was more consistently reduced in amount. Trypsin was a close second.

9 A few cases of gallbladder disease presenting symptoms for less than two years had no appreciable reduction in the amount of enzymes. After two years, the duration of symptoms bears no relation to the degree of reduction of enzymes.

10 Eight cases of cholelithiasis showed an average reduction below normal in the quantity of enzymes corresponding closely to the reduction in the general cholecystitis cases.

CONCLUSIONS

Testing the duodenal secretion for pancreatic enzymes has been generally considered of little value, owing to the extensive range of fluctuation which is usually encountered. When the secretion of an organ can be obtained for examination, such an examination should yield information of value as to the function of that organ. However, no absolutely reliable clinical method has been devised for testing the functional capacity of the pancreas, particularly that part of the pancreas concerned with enzyme production.

By using a simple quantitative method, probably as accurate as any so far devised, we have found a marked reduction in the amount of the pancreatic enzymes in 85 per cent of forty cases of cholecystitis. We feel that this method of examination, when carefully performed, yields information of value concerning the function of the pancreas. A definite reduction in the amount of the pancreatic enzymes in a doubtful case of cholecystitis is additional corroborative evidence in favor of that malady, just as achylia gastrica should suggest the presence of gallbladder disease until the latter can be definitely ruled out.

THE DEMONSTRATION OF TRANSIENT JAUNDICE IN GALLSTONE COLIC[†]

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It is difficult to say how often the symptom jaundice occurs in gall-stone patients. It is a symptom which the patients and their associates take remarkably little notice of, or the statements are so vague that nothing can be made of them. It is also difficult to ascertain how frequently jaundice follows the attacks themselves, and any data will be vitiated if we do not clearly define what we mean by an attack and what we mean by jaundice. If we take an attack to mean a severe attack and jaundice to mean even the slightest sign of the symptom, the frequency of occurrence will be relatively great, and vice versa. I contend that the symptom will occur more often and its diagnostic value, therefore, will be increased by a systematic search for it, that is to say, by looking for it at times when there is a likelihood of its being present and by looking not only for manifest jaundice but also for occult jaundice, by examining for bile pigment in the blood and urobilin in the urine. By thus searching for this symptom, we can derive considerable help in the diagnosis of gallstones from its presence, although I shall show that jaundice is, of course, by no means a sine qua non in the diagnosis of the disease.

I shall begin by discussing the investigation for bile pigment in the blood, and then deal with the examination for urobilinuria—the two methods of investigation which are appropriate for the demonstration of the slight, the doubtful, or the entirely occult forms of jaundice.

The reason for examining the blood for bile pigment is that the increase of bile pigment in the plasma must reach a certain value before it becomes actually visible as jaundice of the skin and sclerotics, and before it is excreted in the urine in quantities that can be detected. The necessary increase in the plasma varies in the different forms of jaundice. It is usually greater in jaundice of a hemolytic nature and smallest in pure obstructive jaundice. But it also depends on the duration of the jaundice which is clearly evident in the case of the urine, for in acute jaundice excretion of bile pigment in the urine more readily takes place while in more chronic cases it is more firmly combined in the plasma and is not so easily excreted. It appears to be a general rule that the bile pigment is present in greater concentration in the plasma than in the tissues and urine in generalized jaundice. As regards the urine, I shall illustrate this point with some examples given in Table 1.

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The amount of bile pigment in the plasma was determined by the dilution method, which I have previously described,¹ the principle of which is that by diluting the plasma until it matches a standard tint we measure how yellow it is. The method is useful and convenient. Values up to 5 are within normal limits, above 5 they represent a pathologic increase.

It will be seen from Table 1 that the different forms of jaundice have high plasma color values, and that if, in the same manner, we measure approximately how yellow the urine is,² we find that, even in cases of most complete obstructive jaundice, the urine is always lighter in color than the plasma, so that other laws are operative in the case of the bile pigment than apply, for example, to sugar, for we measure the blood sugar in parts per thousand but the urine sugar in parts per cent.

TABLE 1.—*Presence of Bile Pigment*

	Plasma	Urine	Rosenblath Test
Hemolytic jaundice	32	< 5	—
Hemolytic jaundice	54	< 5	—
Hemolytic jaundice	41	< 5	—
Pernicious anemia	21	< 5	—
Catarrhal jaundice	44	30	+
Catarrhal jaundice	30	< 5	—
Catarrhal jaundice	100	27*	—
	790	39}	+
Hepatic cirrhosis	26	15	?
Carcinoma of pancreas	190	180	++
Carcinoma of pancreas	84	45	++
Carcinoma of pancreas (?) stone in common bile duct	250	55	++
Carcinoma of stomach, metastases in liver	130	100	++
Carcinoma of stomach, metastases in liver	76	60	++

* On one day the urine was light in color, and on the other it was dark.

1 An account of the method is given in the *Deutsch Arch f klin Med* 132, Parts 5 and 6, 1920, *ibid* 137, Parts 1 and 2, 1921. It is best to use the ready made apparatus (Meulengracht's Bilirubin Colorimeter, manufactured by Paul Altmann, Berlin NW 6 Louisenstrasse 47). It resembles the Sahli hemoglobinometer with two glass tubes and a ground glass plate. One of the tubes contains the faintly yellowish standard solution and serves as a comparison, the other is graduated and is used for the dilution. If the tint of the colorimeter is not good (too greenish) one can prepare a standard tube for oneself with the standard liquid potassium bichromate, 0.05, distilled water, 500, sulphuric acid, 2 drops. The technic is as follows. About 3 c.c. of blood are taken with a dry, sterile cannula from the arm vein into a small test tube in which 2 drops of 3 per cent sodium oxalate solution have been previously put to prevent coagulation. The tube is inverted a few times and placed in a stand for from twelve to twenty-four hours until the blood corpuscles have sedimented, or, if one is in a hurry, it can be centrifugated. With the pipet, 0.5 c.c. of the supernatant plasma is transferred to the tube graduated in two and one-half cubic centimeters. It is then diluted with physiologic sodium chloride solution till it matches the color of the solution in the standard tube. The height of the liquid measured by the graduations of the tube gives the "plasma color value," "bilirubin value" or "jaundice index." If the value is greater than 5, the plasma must be diluted beforehand and the value obtained multiplied by the degree of dilution.

2 It is only a very rough estimation as the color of the urine is not determined by the bile pigment (bilirubin) alone.

When, therefore, one advocates determinations of bile pigment in the plasma in the diagnosis of gallstones, it is because the very slight degrees of jaundice are not visible or are doubtful in the skin and cannot be detected by the excretion of bile pigment in the urine, and, furthermore, the remains of jaundice which is disappearing can be most easily recognized, or only recognized, in this way.

It is true that the acute obstructive jaundice which occurs in connection with gallstones is one of the forms of jaundice in which bile pigment is most readily excreted in the urine.³ But that plasma determinations are useful in spite of this I can show with the help of some examples.

TABLE 2—*Observations in Case 1*

C O, a woman, aged 56, April 24 to Sept 16, 1922, *morbus cordis*, cholelithiasis had previously had similar attacks, while in the hospital for heart disease, a typical gallstone attack occurred.

		Visible	Plasma	Rosenbach Test	Urobilin	
August 27	Pain, vomiting					
August 28		+	32	+	++ }	Temperature raised
August 29		+	28	Trace	++	Trace
August 30		?		—	++	Trace
August 31		?	7	—	++	Trace
September 1		—		—	—	—
September 2		—	6	—	—	—
September 3		—		—	—	—
September 4		—	4	—	—	—
September 5		—		—	—	—
September 6		—	5-4	—	—	—

There was typical tenderness. The feces had no stones and were not clay colored.

If, as a first example, we look at Table 2, we see how an attack with clearly visible jaundice progresses. Jaundice is only present temporarily for a few days after the attack of pain. The plasma color values are increased, bile pigment is excreted in the urine (Rosenbach's test), and there is urobilinuria (Schlesinger's method as well as Marcussen's and

3 In my first publication (*Deutsch Arch f klin Med* **132**, 1920) on bile pigment in the blood, I spoke of a "threshold" for skin jaundice and a "threshold" for the excretion of bile pigment in the urine. I wrote that these boundaries were extremely different in the various forms of jaundice, which is a fact. In the case of the skin and sclerotics, they are commonly about 8, 10, 12 or 15. In the case of the urine, I gave too high values at that time as I had usually investigated chronic forms of jaundice. Subsequently, I have observed that in acute gallstone attacks the excretion of bile pigment may occur in the urine with a plasma color value below 10.

S Hansen's modification in a dilution 1:10) The tests for plasma and urobilin are here superfluous as the jaundice is directly visible

In Table 3, we see a typical example of the necessity of examining the plasma and testing for urobilinuria in order to catch the rapidly disappearing jaundice Nothing was seen in the skin Rosenbach's reaction in the urine was doubtful

I may perhaps venture to say that all these reactions (Gmelin's, Rosenbach's and Troussseau's) for bile pigments in the urine are on the whole, always bad and ambiguous except in the more marked forms of jaundice One investigator will return a positive result and another

TABLE 3—*Observations in Case 2*

A M a woman, aged 36 June 7 to June 20, 1922, cholelithiasis, rehylia gastrica had had attacks for five years had always been treated for achylia had been admitted with this diagnosis She had had a severe attack on the day before admission

	Visible	Plasma	Rosenbach Test Trree	Urobilin
June 8	—	12	Tree	— — —
June 9	—	5	—	— +
June 10	—	4	—	—
June 11				—
June 12				—
June 13	—	3	—	—
June 14				—
June 15				—
June 16				—

There was typical tenderness no stones were present in the feces, and they were not clay colored Operation was done June 28, a number of stones were found in the gallbladder and the cystic duct

a negative result and we resort to a glance at the patient in order to decide by the presence or absence of jaundice whether to call the reaction positive or negative

Table 4 shows quite a similar case There is doubtful jaundice of the sclerotics, as is often the case so that one is undecided about it On examining the plasma, a numerical value is obtained and it is concluded that there has been brief transient jaundice in connection with the pain

Table 5 shows that it is of course not necessary to make a series of investigations but that we may confine ourselves to carrying out a plasma determination and a test for urobilinuria after an attack of pain and then repeat the tests some days later In private practice it will often happen that benefit can be derived from the tests in the consulting room, there has been an attack of pain, and the investigation shows that it has been accompanied by transient occult jaundice

TABLE 4—*Observations in Case 3*

J L, a man, aged 45, August 5 to 14, 1922, cholelithiasis, had never had a previous attack, admitted for abdominal colic, pain began four days before admission, particularly severe pain on admission

		Visible	Plasma	Rosenbach Test	Urobilin	
August 5	Pain	?	10	—	++	Temperature slightly raised
August 6	Pain	?	13	—	+	
August 7		—	6	—	++	
August 8		—		—	+	
August 9		—	3	—	++	
August 10		—		—	+	
August 14		—	3	—	—	

There was slight tenderness, the feces were not clay colored, no stones were present. Subsequently, the patient passed a stone at home.

TABLE 5—*Observations in Case 4*

A J, a woman, aged 31, May 11 to 22, 1921, cholelithiasis, had been treated for some time for gastric disease, four days before admission, had had an attack in the right side, back and shoulder blades, associated with vomiting, had had pain now and again since, admitted for cholelithiasis

		Visible	Plasma	Rosenbach Test	Urobilin	
May 12		—	11	?	+++	Temperature raised
					+	
May 13						
May 14						
May 15						
May 16						
May 17		—	2	—	+	

There was typical tenderness.

TABLE 6—*Observations in Case 5*

E P, a woman, aged 24, April 13 to 23, 1921, cholelithiasis, had had a previous attack four or five days before admission had an attack of pain with vomiting, was admitted for cholelithiasis

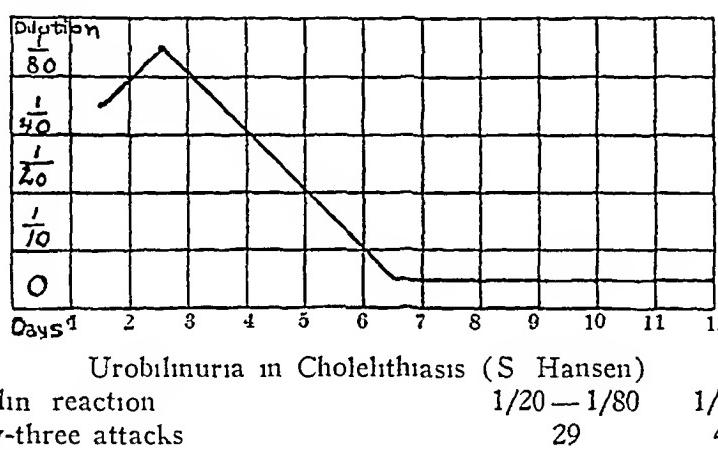
		Visible	Plasma	Rosenbach Test	Urobilin
April 14		—	7	—	+++
					++
April 15		—			
April 16		—	4	—	Trace

There was tenderness in the epigastrium, the temperature was normal.

It is not advisable to give general rules for the standard to be set up for recognizing occult jaundice. Sometimes, one will be inclined to be satisfied with little, as, for instance, in Table 6, when there is reason to believe that one has to deal with the last traces of jaundice, which has been more pronounced on the preceding days but is now disappearing.

From the examples cited, it will be seen how the slight jaundice has been continuously accompanied by urobilinuria. Thanks to S Hansen's article⁴ on urobilinuria in cholelithiasis, it is now generally known that, in the transient urobilinuria following an attack, we possess an excellent aid to diagnosis in cholelithiasis.

In the accompanying chart, I have reproduced the type curve which S Hansen found. He also found urobilinuria with extraordinary regularity after an attack; after twenty-three attacks (comparison should be made with the chart) he discovered an increased excretion of



urobilin in the urine in all cases. He concludes, therefore, that the symptom is "almost constant" after a gallstone attack.⁵ I have, however, been unable to observe such a constancy of the symptom, and I can only explain S Hansen's constant finding as the result of chance, or as an indication that he has been particularly strict with regard to what he will recognize as a gallstone attack, and especially lax with regard to what he will allow to be a positive urobilin reaction, since there is a definite subjective factor involved in adjudicating on them. I shall give some examples below of the absence of urobilinuria in undoubtedly attacks accompanied by slight manifest jaundice or a small increase in the plasma color values (Tables 7 and 8).

I must, therefore, state that genuine attacks may occur without the association of any of the elements of jaundice whatever (Tables 9 and 10).

4 Hansen, S Ugesk f Laeger 82 415 (March 25) 1920

5 Cases of stone in the common bile duct with total shutting off of the intestine are excluded

TABLE 7—*Observations in Case 6*

E P., a woman, aged 55, Nov 27 to Dec 17, 1921, cholelithiasis, obesity, had had a series of attacks at home, described as heart attacks, was admitted for heart disease and obesity, had had attacks for the last two days before admission

	Visible	Plasma	Rosenbach Test	Urobilin	
November 27	+	37	+	+	
November 28	+		+	+	
November 29	+	15	+	+	
November 30	Trace	6	—	+	
December 1	—	7	—	+	
December 2	—	7	—	+	
December 3	—		—	+	
December 4	—	5	—	+	
December 5	—		—	+	
December 6	—	5	—	+	

There was no tenderness, no stones were present in the feces, and they were not clay colored

TABLE 8—*Observations in Case 7*

J L., a woman, aged 32, Nov 26, 1919 to Jan 21, 1920, cholelithiasis, for a year the disease was regarded as colitis, had had attacks of pain, was admitted for colitis

		Visible	Plasma	Rosenbach Test	Urobilin
December 14	Attack of pain				
December 15	Attack of pain				
December 16		Trace	16	—	
December 17		—		—	
December 18		—	6	—	
December 19		—		—	
December 20		—	5	—	
December 21		—		—	
December 22		—	5	—	
December 23		—		—	
December 28		—	4	—	
January 5		—	4	—	

There was fairly typical tenderness, the temperature was normal. An operation was performed January 21. A number of stones the size of hemp seeds were found in the gallbladder

To recapitulate my opinion of the diagnostic value of jaundice in cholelithiasis, I consider that its value is considerably enhanced if the slight or occult degrees are searched for. It will then appear that a considerably larger proportion of the cases than is generally believed are accompanied by slight transient jaundice. But there are, of course, two points on which we must be clear. In the first place, jaundice can mean much more than cholelithiasis. Just as we may be deceived by manifest jaundice into diagnosing cholelithiasis, we may also be led astray by the slighter degrees of jaundice if we hunt for them assiduously and attribute too great diagnostic importance to them. Thus, like

TABLE 9—*Observations in Case 8*

E. J., a woman, aged 33, Oct 4 to 13, 1921, cholelithiasis, had had attacks for ten years, which were diagnosed as gastric disease, was admitted for hepatic colic

	Plasma	Urobilin
October 6	5	—
October 7 Pain		—
October 8 Severe attack		—
October 9 Pain	5	—
October 10		—
October 11	3	—
October 12	5	—
October 13	4	—
October 14		—
October 15	4	—
October 16 Severe attack	4	—
October 17 Pain		—
October 18 Pain	5	—

There had been typical severe attacks, with typical tenderness each time. No stones were in the feces. The temperature was normal. An operation was performed, October 31, two stones the size of a cherry were found in the gallbladder.

others, I have been led on a false scent. The same applies here as to albuminuria which, although it may signify many different things, is nevertheless a valuable aid to diagnosis in nephritis. It should, therefore, only be kept in mind that jaundice, manifest or occult, may also signify other things, such as disease of the liver cells, or it may be of an infectious nature. But what is characteristic of a gallstone attack is that transient jaundice of short duration occurs in conjunction with pain which clinically resembles gallstone colic.

What might at first be expected to cause difficulty is transient jaundice and transient urobilinuria of an infectious nature, that is to say, caused by toxic bacterial action on the liver cells. For this to happen,

however, higher fever or special infections must usually be present, so that these difficulties will not, as a rule, be great in the clinic.

Secondly, as I have mentioned, we must realize that gallstone colic need not be accompanied by jaundice in any of its manifestations (Tables 9 and 10).

When jaundice is manifest, one is spared further investigation and, as a rule, in practical diagnosis one is glad to avoid it as much as possible. But, if it is a question of looking for occult jaundice, it may be asked which of the two methods of investigation is to be preferred, the examination for bile pigment in the plasma or the examination for urobilinuria. Theoretically, the two investigations supplement each other and the urobilinuria may be absent while the other symptom is present. In a well appointed department where skilled assistance is

TABLE 10—*Observations in Case 9*

A A, a woman, aged 33, May 26 to June 20, 1922 cholelithiasis, achylia gastrica had had attacks for three years, was admitted for cholelithiasis (2).

		Visible	Plasma	Rosenbach Test	Urobilin
June 9	Severe attack	—	8	—	—
June 10		—	3	—	—
June 11	Severe attack	—	3	—	—
June 12		—			
June 13		—			
June 14	Severe attack	—	8	—	—
June 15		—	3	—	—
June 16		—			{++}
June 17		—			{+} } Temperature 38.39°C
June 18		—	8	—	{++} {+} —
June 19		—			—

The gallbladder was palpable. No stones were in the feces. There was typical tenderness. Operation was done July 3, two stones were found in the gallbladder, one firmly impacted in the cystic duct.

forthcoming, it may perhaps be a matter of indifference which of the methods is employed or whether both of them are made use of. But in private practice it is otherwise.

The diagnosis cholelithiasis is one which, to a great extent, is made in the home in actual practice, and one cannot, in this case, as in other diseases, leisurely subject the patient to various examinations and so make the diagnosis by steps, but one must strike while the iron is hot and make the diagnosis when the patient has an attack. Whether it is tenderness or jaundice that is searched for, we must seize the opportunity while it is there. Thus, it is of no avail to make use of too complicated apparatus and methods for the demonstration of jaundice which waste time. In this respect, each of the two methods has its advantages and disadvantages. In the examination for urobilinuria,

venipuncture is avoided, this, however, should not entail any difficulties. The examination by Schlesinger's method⁶ will as a rule be adequate when it is only a question of a strong reaction and when it is remembered that the reagent is somewhat altered on keeping. Marcussen and S Hansen's modification⁷ in a dilution 1:10 is likewise fairly simple and rapid. But a disadvantage in a urobilin determination is that a twenty-four hours' sample of urine should really be used because individual samples may vary considerably, partly on account of the changing diuresis and partly on account of variations in the twenty-four hours' excretion.⁸ I myself consider that the plasma determination is convenient and well adapted for the consultation room. It seems to me that, in the consultation room, it is simpler to take a sample of blood than obtain a twenty-four hours' sample of urine, and, with practice, it is only necessary to let the tube with the oxalated blood stand till the blood corpuscles have sedimented. It is then possible to see directly whether the plasma is yellower than it ought to be and it is unnecessary to obtain the actual numerical value.⁹

The chief point, if it is desired to make use of jaundice as the basis of differential diagnosis, is to select the right time, as already pointed out, and the mode of procedure must therefore be to instruct the patient in doubtful cases in which there is a suspicion that he is suffering from gallstones, to present himself or send for the doctor when there has been an attack of pain, so as to afford one the opportunity of investigating whether jaundice in any of its manifestations occurs in direct association with such an attack.

6 Schlesinger's method Equal parts of urine and the vigorously shaken reagent (zinc acetate 10, absolute alcohol 90) are mixed and left to stand for twenty-four hours. Above the flocculent precipitate, there is a column of clear liquid. A green fluorescence in the latter denotes the presence of urobilin. If it is desired to read the result immediately, two or three drops of tincture of iodin (1:20) must be mixed with 10 cc of urine and then filtered. (On the addition of iodin the urobilinogen present is oxidized to urobilin, on standing this takes place spontaneously.) The reading is taken by reflected ordinary daylight, preferably against a dark background. As an excess of zinc is essential, the reagent must be vigorously shaken especially because the zinc acetate powder is transformed into a coarse crystalline mass difficult to disperse, on keeping. Ammoniacal urine should be overneutralized with acetic acid.

7 Marcussen and S Hansen's modification (Ugesk f Laeger 80:16 [Jan 3] 1918) 1 cc urine and 4 cc distilled water and 2 drops of tincture of iodin are mixed together, 5 cc of the reagent (zinc acetate 2, absolute alcohol 100) are added. It is then shaken. The result is read after filtration or on standing.

8 Weltmann, Oscar, and Tenschert, Otto Ueber die Tagesschwankungen im Urobilinogengehalt des Harnes bei Gesunden und Kranken, Wien med Wchnschr 18:766-770, 1922.

9 Hijmans von der Bergh's method for the demonstration of bile pigment in the blood which is now employed extensively is, in my opinion, much too complicated for the present purpose, and it is also subject to large quantitative errors (my paper in the Deutsch Arch f klin Med 137, 1921).

THE AGE CURVE OF PULSE RATE UNDER BASAL CONDITIONS¹

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This study was undertaken with the following ends in view

1 To furnish standards, so far as the available data will permit, of the average normal pulse rate under basal conditions and the extent of normal variations from this average

2 To observe the changes in pulse rate with age and with sex

3 To compare the age curve of pulse rate with the age curve of metabolic rate

Data have been obtained through a survey of the published records of basal metabolism experiments, in which normal subjects were studied

REVIEW OF THE LITERATURE

It is not our purpose to present a complete review of the literature on the subject of pulse frequency. The reader is referred to the work of Tigerstedt¹ for a thorough discussion. Only a few points which appear pertinent to the subject matter of this study will be mentioned.

Average normal values given by Tigerstedt are copied from tables given first by Volkmann,² and based on data collected by Volkmann, Guy³ and Nitsch,⁴ separately. The conditions while not basal were uniform, in that the rates were taken with the subject sitting in a chair, resting, and from two to four hours after the last meal. A number of these average values at various ages are given in Table 1. It will be noted that Volkmann did not give separate values for the two sexes. The general trend of pulse frequency with age according to this table may be summarized as follows: highest in infancy, 134 at 1 year, it drops rapidly at first, reaching 111 at 2 years, then drops more gradually to ninety at 9 and 10 years, seventy-four at 20 years, then remains constant until 55 and rises slightly in old age. These values compare closely with what MacKenzie⁵ offers at birth from 130 to 140, ninety

¹ From the Second Medical (Cornell) Division of Bellevue Hospital, and the Department of Medicine, Cornell University Medical College.

¹ Tigerstedt, R. Die Physiologie des Kreislaufes, Ed 2, Berlin and Leipzig, de Gruyter, 1921, pp 429-472

² Volkmann, A W. Die Haemodynamik, Leipzig, 1850, pp 407-445

³ Guy, W A. The Pulse, in Todd, R B. Cyclopaedia of Anatomy and Physiology 4 181-194, 1847-1849

⁴ Nitsch, quoted from Tavastzerna, A. Zur Kenntnis der Individuellen Schwankungen des Blutdruckes beim gesunden Menschen, Skand Arch f Physiol 21 405-430, 1909

⁵ MacKenzie, James. Diseases of the Heart, Oxford Med Pub, 1908, pp 120-135

at 9 or 10 years, seventy-four at 20 years, from 66 to 76 at from 30 to 50 years with some increase after 50 years. Many other authorities agree closely with Volkmann, showing that his work has been the usual source of statements regarding the normal pulse rate, and that it appears to be confirmed by the findings of clinicians in everyday practice.

Variations within normal limits have been indicated in Volkmann's table by giving the highest and lowest observation at each age, together with the number of observations. There are differences of from 40 to 60 beats per minute, roughly from 20 to 30 per cent above and below the average, slightly greater in youth than in adult life and old age.

TABLE 1—*Comparison of Pulse Rate at Different Ages Under Different Standard Conditions*

Age	Men and Women Not Basil		Men—Basil		Women—Basil	
	from Volkman	Benedict et al	Bruylé	Benedict et al	Bailey	
1	134	116		122		
2	111	104		103		
3	108	92		86		
4	108		100	87	99	
5	103		91	91	88	
6	98	87	97	80	97	
7	93	85	92	73	92	
8	94	80	100	77	101	
9	89	81	93	85	100	
10	91	79	84	80	92	
11	87	75	84		92	
12	89	69	90	80	89	
13	88	76	87	82	86	
14	87	75	83	79	81	
15	82	70	77	77	82	
16	83	71	77	77	83	
17	80	68	74	72	78	
18	76		76	73	78	
19	77	65	77	71	78	
20	74	64	73	69	74	
20-40	71	62	75	68	77	
40-60	73	57	70	70	74	
60-70	74	66	66	71	78	
70 and over	75	65		73		

Sex was clearly shown by Guy⁵ to produce a difference in pulse rate. At every age after 2 years the females of his series have a more rapid rate than the males, the difference being slight up to 7 years, after that from 6 to 14 beats per minute with an average of 9 beats per minute. Friberger⁶ gives a table of the average pulse rate of boys and of girls from 6 to 15 years of age, in which the difference in the sexes averages 11 beats per minute. Volkmann,² on the other hand, showed that when women and men of the same body length were compared, there was no constant difference. He ascribes the difference noted by Guy and others to body size and draws analogies from the animal kingdom, large animals having slower, small animals having faster pulse rates. The validity of these arguments has been somewhat

6 Friberger, R. Ueber die Entwicklung von Puls und Blutdruck im spateren Kindesalters, Arch f Kinderh 60 331-339, 1913.

lessened by more recent work Benedict⁷ has used the biometrical method of correlation coefficients, to find what relationship stature and pulse rate may have to one another and states "As far as available data justify conclusions concerning the problem, they seem to indicate that there is only a very slight if any interdependence between stature and minimum or basal pulse rate in man"

Age, it appears, plays a definite part in the differences in pulse frequency Volkmann showed that persons of the same size, but younger, have more rapid pulses

Tigerstedt¹ considers the variety and number of factors which influence the pulse rate in normal persons Muscular exertion is the principal one All manner of external stimuli, even internal stimuli such as produced by body processes or emotions have immediate and marked effect In commenting on the data of Volkmann, Guy and Nitsch, he says that had the subjects been at more nearly perfect rest the average values would be lower He quotes several observers on the effect of rest on the pulse rate Aulo⁸ showed that there was a gradual fall of the pulse rate during rest to a level reached after from eighty to one hundred minutes At what appeared to be complete rest, with a curve the average point of which remained constant at about 50 beats per minute, variations continued to occur from minute to minute as great as 10 per cent above and below the average We find no other data which indicate the occurrence of variations as great as those noted by Aulo Bleuler and Lehmann⁹ counted the pulse of a subject every five or ten minutes, from 8 25 a m to 8 12 p m, and found that the rate varied from 59 to 64, about 5 per cent above and below the average It is a common experience in basal metabolism work to find variations of from 1 to 5 beats per minute in repeated counts after the patient has rested for thirty minutes This would indicate that Aulo's subjects were extraordinary in the variability of their pulse rates, or that the resting conditions were not so complete as those which are required in basal metabolism determinations Aulo showed that the fall in pulse rate during sleep was approximately the same in amount as that at complete rest, but that during sleep the fall occurred more quickly Klewitz¹⁰ states that during the day there is no difference in the pulse of subjects asleep and the pulse of subjects awake and at rest, but that at

7 Harris, J A, and Benedict, F G A Biometric Study of Basal Metabolism in Man, Publication 279, Carnegie Institute, 1919

8 Aulo, T A Zur Kenntnis der Pulsfrequenz des Menschen bei Muskelruhe und im Schlaf, Skand Arch f Physiol **21** 266-276, 1909

9 Bleuler, E, and Lehmann, K B Ueber einige wenig beachtete wichtige Einflusse auf die Pulszahl des gesunden Menschen, Arch f Hyg **3** 215-248, 1885

10 Klewitz, F Der Puls im Schlaf, Deutsch Arch f klin Med **112** 38-55, 1913

night during sleep a greater fall occurs Korosy¹¹ made the observation that a group of soldiers between the ages of 20 and 24 had an average pulse rate of 63.3 These men were resting quietly in bed in the morning A short interval was allowed to elapse after they were wakened and no food was given The conditions may be considered basal He calls attention to the fact that the average is lower than that obtained by Volkmann,² Guy,³ Nitsch,⁴ Quetelet,¹² Vierordt¹³ and others whose conditions were not basal

In recent years, the workers on metabolism have collected a large amount of data on the pulse frequency under basal conditions In basal metabolism work, the observations are made with the subject in the postabsorptive and resting state, the fall in pulse rate to a constant level being one of the criteria of the length of rest required The largest amount of this work has been done by Benedict¹⁴ and his co-workers of the Nutrition Laboratory of the Carnegie Institution of Washington Detailed discussions of the basal pulse rate may be found in the publications of the Carnegie Institution dealing with infants, older children and adults

Infants studied by Benedict and Talbot¹⁴ during the first 5 days of life showed a slight progressive decrease during the first 3 days, then a return to the original or a slightly higher level The rates showed a marked drop from the fetal average of 135 beats per minute to an average of 112 beats per minute the first day after birth The fetal pulse was studied first by Kegaradec,¹⁵ whose original observations have been confirmed by many different workers Naegele,¹⁶ in 600 observations, finds the extremes to range from 90 to 180, with an average of from 130 to 140 Premature infants have been studied by Talbot, Sisson and Moriarty¹⁷ The infants were estimated to be from forty-three to 108 days premature Pulse rates ranged from 110 to 185 with an average of 140 to 150, much faster than those of either the fetus or new-born children

11 Korosy, K Studien über Puls und Atmungsfrequenz, Deutsch Arch f klin Med **101** 267-282, 1911

12 Quetelet, A Anthropometrie, Bruxelles, 1870, pp 370-374

13 Vierordt, H Anatomische, Physiologische, und Physikalische Daten und Tabellen, Ed 3, Fischer, Jena, 1906, pp 230-237

14 Benedict, F G, and Talbot, F B The Physiology of the New-Born Infant, Pub 233, Carnegie Inst, 1915 Benedict, F G, and Talbot, F B Metabolism from Birth to Puberty, Pub 302, Carnegie Inst, 1921 Harris, J A, and Benedict, F G A Biometric Study of Basal Metabolism in Man, Pub 279, Carnegie Inst, 1919

15 Kegaradec Memoire sur l'auscultation appliquee a l'étude de la grossesse, Paris, 1822 (quoted in Williams' Obstetrics, Ed 5, 1923, p 207)

16 Naegele, O V Die geburtshilfliche Auscultation, Mainz, 1838, p 35 (also in Preyer Die spezielle Physiologie des Embryo, 1885, p 43)

17 Talbot, Fritz B, Sisson, Warren R, and Moriarty, Margaret L Basal Metabolism of Prematurity, Am J Dis Child **26** 29-55 (July) 1923

During the first year of life pulse rates appeared from the work of Benedict and Talbot¹⁴ to remain approximately the same. A definite trend downward is observed to begin in most of the individual subjects at any point from the fourth to the fourteenth month. In all it appeared before the eighteenth month.

The decrease in childhood is shown by averages selected by Benedict and Talbot¹⁴:

TABLE 2—Decrease of Pulse Rate in Childhood (Benedict)

Age	Pulse Rate	Age	Pulse Rate
1	121	7	78
2	100	8	78
3	89	9	82
4	87	10	81
5	91	12	72

The drop shows many irregularities, as at 5 years and 9 and 10 years, differing in this respect from the uniform curve produced by the data of Volkmann,² Guy,³ and Nitsch.⁴

The effect of sex on the pulse rate is definitely shown in Benedict and Talbot's observations on children only in those under 1 year of age. Girls have higher rates from 1½ to 10 months. There is a tendency to a higher rate in girls than boys in the data from 1 year to puberty, however, fifteen of twenty-six age periods show girls higher while eleven show boys higher. Benedict and Talbot¹⁴ say "On the whole, the picture cannot be said to speak for a higher pulse rate with girls than with boys."

In adults, the grand averages of Harris and Benedict's⁷ cases show a marked difference between the sexes. One hundred and twenty men averaged 61.26 beats per minute, while ninety women averaged 68.87 beats per minute. These figures are remarkably constant in the different sections of the large groups done at separate times and places and by different men. This indicates an average difference in adult men and women of 7.6 beats per minute with sex.

Other men have studied the pulse under basal conditions. Addis,¹⁸ working with soldiers aged from 21 to 23, under basal conditions finds an average of 63 beats per minute and under conditions not basal an average of 80 beats per minute. He shows the variability of the pulse under basal conditions by the odds against the appearance in his series of a given rate higher than the average. For instance, Addis says that the chances that a rate of 88 is normal are only 1 in 1,000. Peterson and Walter¹⁹ summarize 2,500 basal observations on 1,200 clinic

18 Addis, T. Blood Pressure and Pulse Rate Levels, Arch Int Med 29 539-553 (April) 1922

19 Peterson, Anne, and Walter, Will. Basal Metabolism and Ideal Weight and Pulse Ratios, J A M A 78 341-343 (Feb 4) 1922

patients, and find the average for men 66, for women 74. These may be compared to the clinic patients observed by Bailey, mentioned later. In regard to variations Peterson and Walter state that a rate of over 82 in men or over 90 in women is cause for suspicion of hyperthyroidism.

The relation between pulse and age has been taken up by Harris and Benedict¹ in addition to the data given in the foregoing on changes in childhood. The method of correlation coefficients was used on the data of the Nutrition Laboratory for adults 120 men ranging from 16 to 67 years, but mainly between 20 and 35, and ninety women ranging from 15 to 74, but mainly between 20 and 30. They found that there was a slight negative correlation, indicating a decrease in pulse rate with advancing age, in this age group. Harris and Benedict¹ say in regard to this "The amount of change is so small that its nature has not been investigated." They quote Whiting's correlations of the same factors, pulse and age, using data gathered by Goring on prisoners, but not under basal conditions. His results indicate a positive correlation, an increase with age. Benedict suggests that without basal conditions and possibly the presence of increased lability of the pulse with age these contradictory findings of Whiting may be explained.

The investigation of the relationship of the technic and apparatus concerned in the taking of basal metabolism measurements to the results obtained, has yielded some interesting observations on the effect of mixtures rich in oxygen on the pulse rate. Benedict and Higgins²⁰ found a slight, but perceptible fall in rate with the use of air mixtures for breathing, containing 60 per cent oxygen, and a definite drop of about 4 beats per minute when 80 per cent oxygen was used. Parkinson,²¹ and Schneider and Sisco,²² also observed a drop in pulse rate, but only with the use of high percentages of oxygen. Since the oxygen, even in the closed circuit apparatus of the recent portable type almost never rises to 60 per cent, interference with any of the observations used in this study is not likely.

Metabolism and pulse rate have been studied for possible relationship by a number of men. Murlin and Greer²³ showed that pulse rate has less relation to oxygen absorption than the product used to express total heart action, pulse pressure multiplied by pulse rate.

20 Benedict, F. G., and Higgins, H. L. Effects on Men at Rest of Breathing Oxygen-Rich Gas Mixtures, *Am J Physiol* **28** 1-18, 1911.

21 Parkinson, John. The Effect of the Inhalation of Oxygen on the Rate of the Pulse in Health, *J Physiol* **44** 54-58, 1912.

22 Schneider, E. C., and Sisco, D. L. The Circulation of the Blood in Man at High Altitudes, *Am J Physiol* **34** 1-47, 1914.

23 Murlin, J. R., and Greer, J. R. The Relation of Heart Action to the Respiratory Mechanism, *Am J Physiol* **33** 253-282, 1914.

Benedict and Cathcart²⁴ showed that pulse rate and heat production are not proportional in greater muscular activity Murlin and Hoobler²⁵ state that under the same conditions in the same person, minor fluctuations in muscular activity are accompanied by minor fluctuations in pulse rate and basal metabolic rate, but that at different ages in the same infant, this does not hold true A certain infant, sleeping, showed a pulse of 140, at the age of 2 months, and a pulse of 112 at the age of 12 months, while the heat production at the latter age amounted to twice that of the earlier age Harris and Benedict⁷ cite the fact that women have a higher pulse rate than men and at the same time a lower metabolic rate as indicating that "the average pulse rate may have little if any connection with average heat production in a group of individuals" Benedict and Talbot,¹⁴ by an elaborate series of kymographic observations of infants' movements taken during the periods of metabolism experiments, were able to observe that the metabolism varies closely with the movements and pulse rate varies closely with both The record of the pulse rate proved a better practical guide to the changes in metabolism than the record of movements They conclude that in a given infant, variations of pulse rate do accompany variations in metabolism Sturgis,²⁶ in observations of one patient with hyperthyroidism through 192 consecutive days, observed that the resting pulse rate indicated the changes which occurred in the metabolism with few exceptions It appears to be the general opinion among metabolism workers who study hyperthyroid cases, that when the relation of pulse rate to metabolic rate is once learned in a given case, changes in metabolism may be noted with a fair degree of certainty at a subsequent time (Means and Aub,²⁷ and others) In different persons the relationship of pulse to basal metabolism is not comparable, however From a consideration of the opinions of these authors there seems to be no true relationship between basal pulse rate and basal metabolic rate, except in the individual

On the other hand, Harris and Benedict,⁷ again using correlation coefficients, with the data of the adult series before mentioned, find a slight positive correlation between pulse rate and total heat production The degree of correlation is increased by the use of calories per square meter of body surface, thus correcting for the differences in the size of

24 Benedict, F G , and Cathcart, E P Muscular Work, Pub 187, Carnegie Inst, 1913

25 Murlin, J R , and Hoobler, R B The Energy Metabolism of Ten Hospital Children, Am J Dis Child 9 81-119 (Feb) 1915

26 Sturgis, Cyrus C Observations on One Hundred and Ninety-Two Consecutive Days of Basal Metabolism, Food Intake, Pulse Rate, and Body Weight in a Patient with Exophthalmic Goiter, Arch Int Med 32 50-73 (July) 1923

27 Means, J H , and Aub, J C Basal Metabolism in Exophthalmic Goiter, Arch Int Med 24 645 (Dec) 1919

the subjects. Since the correlation is positive in sign it indicates that pulse rate is higher with higher metabolic rates and vice versa in adults. Read²⁸ has also used the method of correlation coefficients with the factors, pulse pressure, pulse rate and basal metabolic rate in a series of 300 observations in thyroid patients and thyroid suspects. He found a high correlation of both pulse rate and pulse pressure with metabolic rate, and with the resulting formula he calculated the metabolic rate in his own series of cases from observed pulse pressure and pulse rate within 10 per cent of the actual value found in 60 per cent of the cases and within 20 per cent in 91 per cent of the cases. This tends to show that in thyroid states at least the pulse rate and pulse pressure have a considerable and fairly constant relation to basal metabolism.

This review of the literature in regard to pulse rates under basal conditions indicates that there is a use and a need for standards of average normal values. Hobson,²⁹ writing in 1923, says "No absolute values can be attached to the observations (pulse) since we have nothing but the crudest guides as to the normal pulse rate." Sturgis and Tompkins,³⁰ on finding in three hyperthyroid patients, after treatments, but with normal metabolism, pulse rates of 57, 55 and 52, considered these abnormally low. It will be shown in the data given below that pulse rates of this order are not infrequent.

SOURCE OF MATERIAL

Unfortunately, we could not base our data on a sufficient number of personal observations, and therefore it is necessary to give the sources from which we gathered material. The work of Benedict and his associates in Boston is particularly valuable, as the purpose of this work was to study normal persons under basal conditions. Practically all of the figures on infants, and many of those on adult men and women come from this source. The subjects were all chosen as normal controls, and were studied in the postabsorptive state, at least twelve hours after the last meal, lying quietly after a rest of at least half an hour. The exception to this is the infants, who were studied immediately after a feeding for the reason that they were quiet at no other time, and quiet is more important than the effect of food. One very interesting set of observations, the studies of the girl scouts, we did not consider comparable with the other work and were forced to omit. These groups of twelve girls occupied a large respiration cham-

28 Read, J. M. Correlation of Basal Metabolic Rate with Pulse Rate and Pulse Pressure, *J. A. M. A.* **78** 1887-1889 (June 17) 1922.

29 Hobson, F. G. A Comparative Study of Basal Metabolism in Normal Men, *Quart. J. Med.* **16** 363-389 (July) 1923.

30 Sturgis, Cyrus C., and Tompkins, Edna H. A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, *Arch. Int. Med.* **26** 467-476 (Oct.) 1920.

ber for the night. The girls were warned to be quiet in the morning and the pulse was counted twice before they got up or had breakfast.³¹ The conditions as regards rest and food were basal, but the two counts show such wide variations as to indicate that, in spite of the advice as to quiet, there was probably a large factor of excitement. In a second series³² the pulse was counted during sleep, giving figures which probably represent the minimal pulse rate, but which are hardly comparable with counts made while the subject is awake. Other figures were obtained from the studies of normal persons made by Magnus-Levy and Falk³³ (who studied basal metabolism using the Geppert-Zuntz method as described in Pfluger's Archives), by Palmer, Means, and Gamble,³⁴ by Blunt and Dye,³⁵ and by Hobson²⁹ (working with the Benedict apparatus), and by DuBois³⁶ and his associates in their studies with the Sage calorimeter. These workers all describe their methods in detail, and no figures were used unless it seemed quite clear that the conditions were basal and the subjects normal. Exception has been taken to the conditions under which DuBois studied the boy scouts. These were unusually vigorous boys, who came into the city from the suburbs, and who had a small breakfast at 6:30 or 7:00 a.m., three or four hours before the experimental period. Soderstrom, Bari and DuBois have shown that such a breakfast does not affect the metabolism after two or three hours, and DuBois states that the

31 Benedict, F G, and Hendry, M F. The Energy Requirements of Girls from 12 to 17 Years of Age, Boston M & S J **184** 217-230, 257-262, 282-286, 297-306, 329-334, 1921.

32 Benedict, F G. The Basal Metabolism of Young Girls, Boston M & S J **188** 127-138 (Feb 1) 1923.

33 Magnus-Levy, A. Ueber Aufgaben und Bedeutung von Respirationsversuchen fur die Pathologie des Stoffwechsels, Ztschr f klin Med **33** 258-268, 1897, Untersuchungen zur Schilddrusenfrage, Ztschr f klin Med **33** 269-314, 1897. Magnus-Levy, A., and Falk, E. Der Lungengaswechsel des Menschen in den verschiedenen Alterstufen, Arch f Physiol, 1899, supplement, pp 314-367.

34 Palmer, W W, Means, J H, and Gamble, J L. Basal Metabolism and Creatinin Elimination, J Biol Chem **19** 239-244, 1914.

35 Blunt, K, and Dye, M. Basal Metabolism of Normal Women, J Biol Chem **47** 69-87 (June) 1921.

36 Gephart, F C, and DuBois, E F. The Determination of the Basal Metabolism of Normal Men and the Effects of Food, Arch Int Med **15** 835-867 (May) 1915. Soderstrom, G F, Meyer, A L, and DuBois, E F. A Comparison of the Metabolism of Men Flat in Bed and Sitting in a Steamer Chair, Arch Int Med **17** 872-886 (June) 1916. DuBois, E F. The Metabolism of Boys Twelve and Thirteen Years Old Compared with the Metabolism at Other Ages, Arch Int Med **17** 887-901 (June) 1916. Gephart, F C, and DuBois, E F. The Basal Metabolism of Normal Adults with Special Reference to the Surface Area, Arch Int Med **17** 902-914 (June) 1916. Aub, J C, and DuBois, E F. The Basal Metabolism of Old Men, Arch Int Med **19** 823-831 (May) 1917. Soderstrom, G F, Barr, D P, and DuBois, E F. The Effect of a Small Breakfast on Heat Production, Arch Int Med **21** 613-620 (May) 1918. Olmstead, W H, Barr, D P, and DuBois, E F. Metabolism of Boys Twelve and Fourteen Years Old, Arch Int Med **21** 621 (May) 1918.

boys were quiet, being allowed to read for part of the experimental period Benedict,¹⁴ while he does not criticize the breakfast allowed the boys, states that in the first series muscle activity caused such great irregularities in metabolism (sometimes a difference of 12 per cent in successive hours) that the conditions cannot be considered basal. He accepts the experimental conditions of the second series.

By some of the observers the pulse was counted with a stethoscope while by others it was counted at the wrist. Theoretically, in every case the count should be made without the subject's knowledge, practically with careful work, it seems to make little difference. In examining the records the relative constancy of the basal pulse rate from minute to minute is very striking. In fact, when there are marked variations, one suspects that the conditions were not truly basal.

PRESENTATION OF DATA

In assembling our data we have tried to show the findings by a series of charts constructed to show the pulse rates observed for each year, both in males and in females. These charts are constructed on the same scale, using years as abscissas, in each case the age being taken as that of the nearest birthday,¹⁷ and pulse rates as ordinates. The base line is placed at 40 because a pulse of 0 is impossible and because it is said that a pulse of less than 40 should arouse a suspicion of heart block.¹⁸ Each observation is put down with a symbol to indicate the observer, and a line is drawn to show the general average. This line is drawn by inspection, not showing the actual arithmetic average for each year, these averages being given in Table 1, but attempting to indicate the general trend. We believe that this is a fair procedure and one which shows the situation more accurately than if we gave the sharp up and down variations as they appear from year to year. There is no reason to believe that these zigzag variations actually occur, and were the series of cases larger, they would doubtless disappear as in Volkmann's² series. As we shall try to make clear in the comment the position of the line in puberty and in old age is open to question. We have drawn the line tentatively on the basis of present information, realizing that it is open to revision when more adequate reports are available.

Table 1 compares the average pulse rate, not basal, for a large series of normal persons, male and female, with the basal pulse rates of normal controls and of objectively healthy clinic patients. The first series is taken from Volkmann,² the figures for the normal controls under basal

37 An exception was made in the case of one man and two women over 80. Here the age was considered to be 80.

38 Lewis, Thomas. *Clinical Disorders of the Heart Beat*, Ed. 5, New York, Paul B. Hoeber, 1921, p. 5.

conditions are the averages of the observations shown in the charts, while the basal pulse rates of clinic patients were obtained through Dr C V Bailey, of the Post-Graduate Hospital.

Charts 1 and 2 show the pulse rates of males between the ages of 1 and 80, with the average drawn in as explained in the foregoing. Certain points are evident on inspection of the chart, namely, the rapid

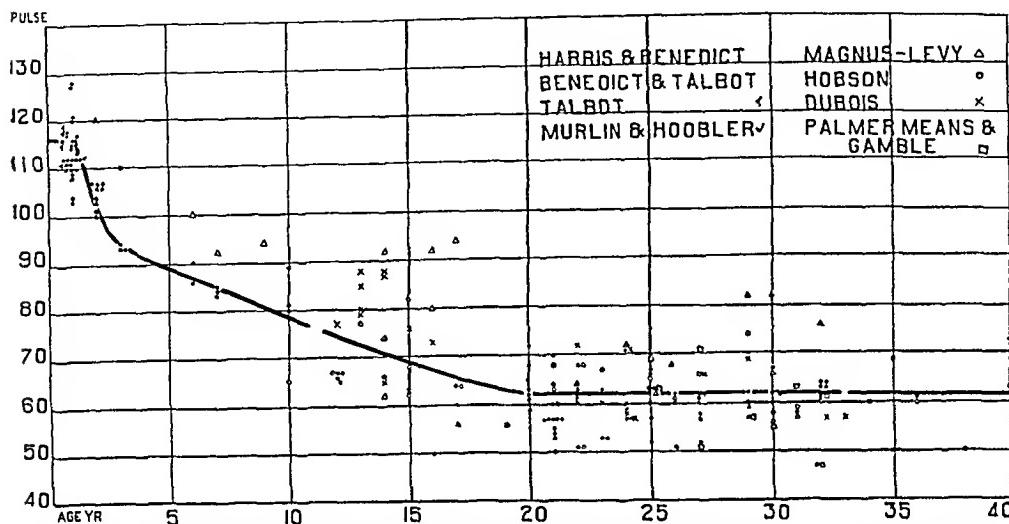


Chart 1—Curve of basal pulse rate in relation to age for males, aged from 1 to 40 years. Source of the data is indicated by symbols.

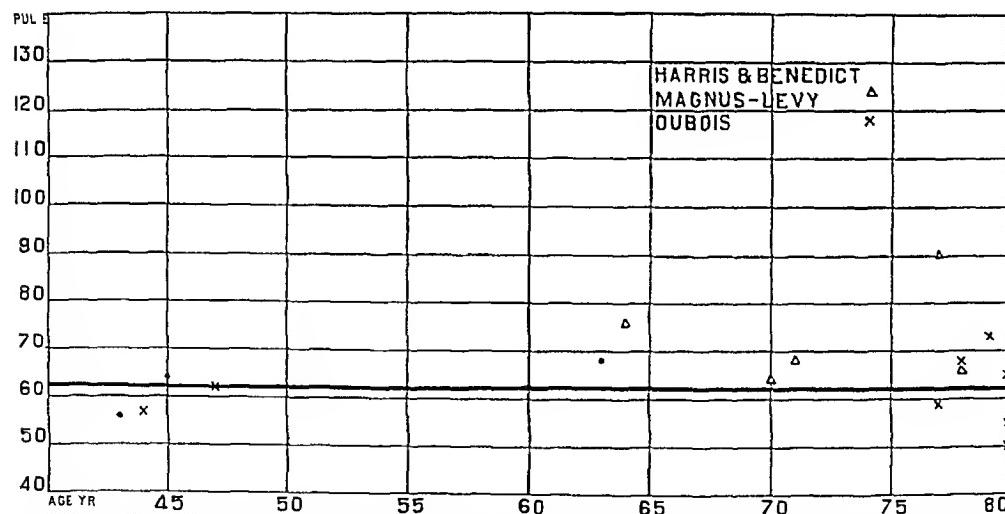


Chart 2—Curve of basal pulse rate in relation to age for males, aged from 40 to 80 years. Source of the data is indicated by symbols.

drop during infancy with a more gradual decline during childhood and youth to the adult level of 62 at 20 years, at which point the pulse remains constant throughout the greater part of adult life with a possible slight tendency to rise in old age. It also shows the common range of variations and the greater, less common variations. Other points will be discussed in more detail later.

Charts 3 and 4 show the same thing for females. Again one notes the rapid drop in early childhood and the more gradual decline during later childhood. The adult level, reached at the age of 20 is 69, 7 beats higher than the average for adult men. The variations seem somewhat more marked than in the case of the men, and there is a paucity of observations after 35 years which makes the later averages of doubtful value.

COMMENT ON DATA

In order to study the starting point of the curve, we studied the pulse rate at birth and for the first 18 months of life. Most of the figures for this period are taken from Benedict and Talbot,¹⁴ and we have nothing to add to what they have already said and shown. At birth they found the average pulse rate to be 112, a rate considerably lower than the 130 to 140 usually given as the average for the fetus. During the first week the rate rose approximately to that which we find at the end of the first year. During this year the rate varies in different persons and at different months, but there is no evidence of a definite trend, and the monthly variations seem to be without significance. In taking the averages for the year, we followed the rule which we had adopted for the other ages, using the rates for the months which were nearest to the first birthday. Thus we found the average to be 116 for boys and 122 for girls. The reason for this difference is not clear. Townsend,¹⁹ in a series of 1,000 cases, found the average pulse rate at full term to be 140.26 for boys and 141.83 for girls. As there is no constant difference during the succeeding years, it seems a curious coincidence that the sex difference at one year should correspond so closely to the difference that we find in adult life.

At the other end of life the figures are very unsatisfactory, as few observations have been made on the pulse rate of the aged. We have no such series of cases as was reported by Pennock,⁴⁰ who studied 173 men between the ages of 50 and 90, and 203 women between the ages of 50 and 115. Our figures show a very slight increase in the pulse rate of old women and an almost negligible increase in that of the old men. As it is usually stated that the pulse rises slightly in old age, it may be worth while to give Pennock's figures, which, representing pulse rates under uniform but not basal conditions, are comparable only within his own series.

39 Townsend, C W. Some Statistics on the Weight of Infants, Sex and Fetal Heart Rate, Boston M & S J 134 484-485, 1896

40 Pennock, C W. Note on the Frequency of the Pulse and Respiration of the Aged, Am J M Sc 40 (os) or 14 (ns) 68-75, 1847

TABLE 3—Pulse Rate of Old Age (Pennock)

Age	Men		Women	
	No. of Cases	Pulse	No. of Cases	Pulse
50- 60	59	70.04	36	73.55
60- 70	58	69.04	68	75.19
70- 80	35	70.04	55	78.28
80- 90	18	72.49	37	75.35
90-115			7	76.56

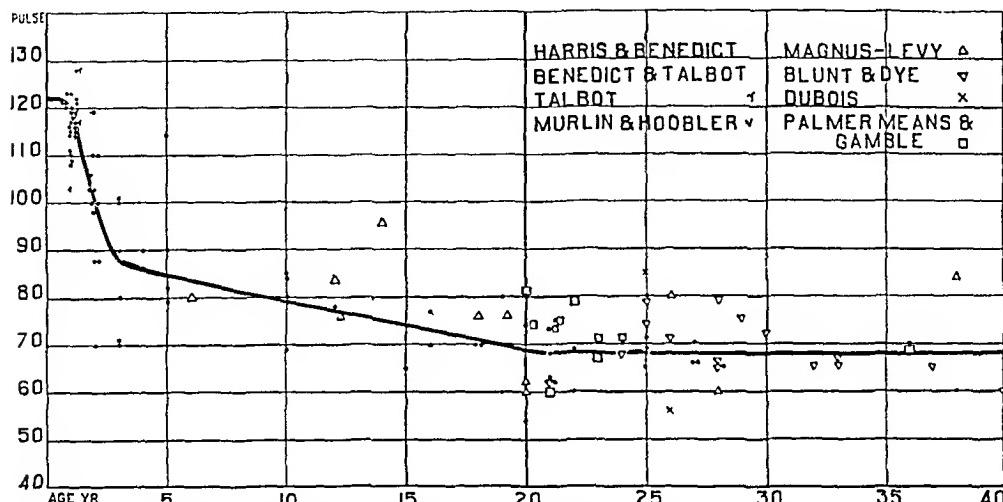


Chart 3—Curve of basal pulse rate in relation to age for females, aged from 1 to 40 years. Source of data is indicated by symbols

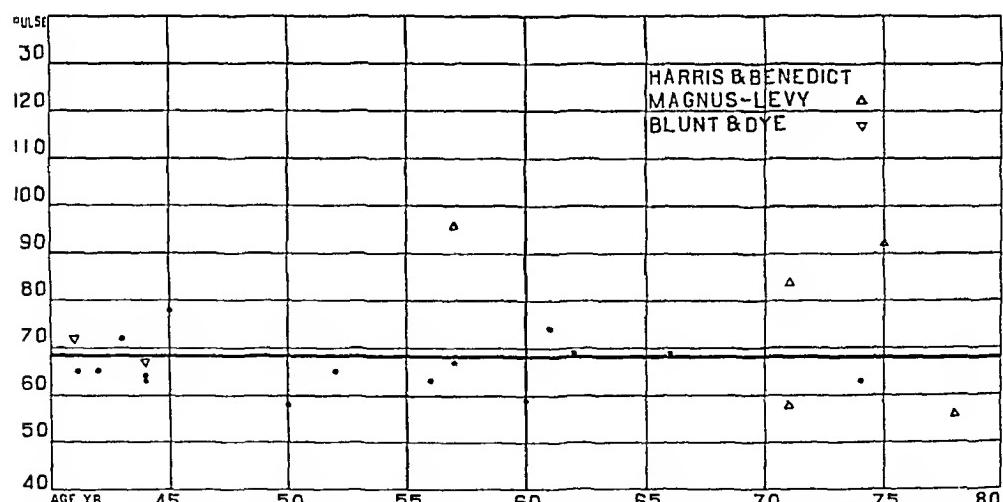


Chart 4—Curve of basal pulse rate in relation to age for females, aged from 40 to 80 years. Source of data is indicated by symbols

The differences certainly are not marked, and the question of determining which persons of this age have a normal circulatory system is difficult. Harris and Benedict⁷ criticized DuBois' ³⁶ old men as being abnormally healthy, and it is more than likely that no man over 60 is perfectly normal. Guy³ realized this difficulty when he stated that the pulse rose in age, if feeble as well as robust men were studied.

The years between infancy and old age are those with which we are chiefly concerned, and it is during these years that the pulse rate is of special interest. We find the basal pulse rate to be 62 for adult men and 69 for adult women, figures which correspond closely with those given by Harris and Benedict,⁷ by Addis,¹⁸ by Korosy,¹¹ and by Blunt and Dye.¹ These figures are lower than those given by persons who studied the pulse under resting but not basal conditions, a finding which was predicted by Tigerstedt.¹ As the resting conditions given by different observers vary, it is obvious that different groups of observations are not comparable, and that in establishing a standard it is necessary to make the observations under standard conditions. As the conditions required for basal metabolism work are well known and widely used they seem the logical conditions to adopt. In speaking of the basal pulse rate basal must not be interpreted to mean minimal for lower rates have been observed during sleep.¹⁰ A detailed study of the sleeping pulse rate would be interesting, but difficult to carry out in a large series, and scarcely applicable to general use. The use of the basal pulse rate would make it evident that many careful studies undertaken to show the normal pulse rate give no indication of the resting normal, but instead show that, for one reason or another, the subjects were not in a state of rest. This applies not only to the older work but to much recent work as that of Burlage,⁴¹ who gives average pulse rates for a series of 1,700 girls and finds rates which are obviously high possibly indicating that the examination caused a good deal of mental disturbance. Basal pulse standards would be of value as a starting point from which to determine the influence on the pulse rate of various factors.

The adult level is reached in both sexes at the age of 20, after a decrease in rate throughout childhood and adolescence. This decrease is more marked in the first two years and less marked later. Owing to the discussion (DuBois and Benedict) as to whether there is an increase in metabolism at or just before the time of puberty, the pulse rate at this time is interesting (Table 1). The figures of Volkmann,² which are not basal and which include observations made on boys and girls, show a continuous drop to the eleventh year, a very slight rise at the twelfth year with an almost constant rate for the next two years, followed by a progressive drop to 20 years. In this series the probability of variations is reduced by the fact that for any year there are from 54 to 107 observations. Katzenberger⁴² shows no rise at puberty for either sex, either in his observations or in the figures which

41 Burlage, S R. Blood Pressure and Heart Rate in Girls During Adolescence, *Am J Physiol* 64: 252-284 (April) 1923.

42 Katzenberger, A. Puls und Blutdruck bei gesunden Kindern, *Ztschr f Kinderh* 9: 167-195, 1913.

he collected from various sources Our figures for boys show a rise at the thirteenth and fourteenth years, but the number of observations is small and most of them are those observations on the boy scouts³⁶ which Benedict¹⁴ criticized as not made under basal conditions A similar rise is observed in the case of Bailey's figures for clinic patients We can show no rise for girls, but it is interesting to note that if we included Benedict and Hendry's³¹ figures on the waking girl scouts, such a rise would be present, while if we used the figures obtained while the girls slept,³² there would be a definite drop In order to settle this question we believe that it is necessary to have a large number of notes made by one observer under strictly basal conditions

For each period we must note, not only the average pulse rate, but the usual range of variations, realizing that this does not represent the limits of normal variation, but the ordinary differences which one is likely to find in any group of persons As MacKenzie⁵ says "The pulse rate varies very considerably according to age, sex and individual peculiarities" Guy³ gave the usual range of variation as 43 beats for men and 48 beats for women, but much greater variations are noted This variation is shown in the charts and scarcely needs comment In men, the usual pulse is between 50 and 70, a total range of 20 beats, rates under 50 and over 80 are decidedly uncommon In women the usual pulse is between 60 and 80 beats to the minute, rates between 50 and 60 and between 80 and 90 occur occasionally, rates over 90 are rare, and no rate less than 50 was observed in this series In a larger series it is probable that in a few cases a wider variation would be noted For the first year the rates, for boys and girls alike are grouped between 108 and 128, but wide variations are noted, the range for boys being from 95 to 145, for girls from 84 to 165 During the second year the extreme variations for boys are from 84 to 127, for girls from 70 to 132 In the third year no rate over 110 was noted for either sex

The difference between the pulse rate of men and of women is a matter of common knowledge and everyday observation This difference does not depend on activity, but exists under basal conditions In women the effect on the pulse rate of the menstrual cycle⁴³ has been considered and found to be inconstant or negligible, therefore it need not be considered in discussing these curves The sex difference in pulse rate in childhood is very slight, and from the second to the tenth year we are able to show no constant and convincing difference⁴⁴ After that, the rate is six or seven beats higher in the female, a difference which is rather less than we find given in most of the references

43 Zuntz, L Untersuchen über den Einfluss der Ovarien auf den Stoffwechsel, Arch f Gynak **78** 106-136, 1906

44 Observations made by us since writing the foregoing indicate that there is a sex difference in the average basal pulse rate below the age of 10 years

in the literature Guy³ gives a difference of from 6 to 14 beats at different periods, the average being 9. The important point, however, is not the numerical difference, simply the fact, long recognized, that the pulse of women is slightly more rapid and slightly more variable than that of men.

Through the kindness of Dr Cameron V Bailey of the Post-Graduate Hospital, we had access to his figures on a large series of basal metabolism determinations. Omitting all patients with a definite diagnosis, an abnormal metabolism, or any thyroid or cardiac disturbance, we obtained data on 301 supposedly normal males between the ages of 4 and 67, and 364 females between the ages of 4 and 68. We did not include these figures in our series because persons referred to a clinic are not those who would be selected as normal controls. We have used these figures for purposes of comparison, and find that the curve representing the average pulse rates for different years follows the same line as that for the normal controls but that it is always from 6 to 12 beats higher. The average for adult men is 73, 11 beats higher than that for the normal controls, while the average for women is 77 as compared with 68. There appears to be a slight rise at the time of puberty in the case of the boys, but no rise is noted in the case of the girls. The range of variations is slightly greater in the clinic patients than in normal subjects. The reason for these differences is not perfectly clear, but it may be that minor disturbances of the type which cause a patient some trouble but which remain undiagnosed by the doctor will cause a slight acceleration of the pulse rate. Possibly it is due to nervousness, the clinic patient expecting the doctor to find something wrong with him, while the normal control consents to the test to oblige the doctor.

The age curves of basal pulse rate and basal metabolic rate have been brought together in Chart 5 for purposes of comparison. The curve of metabolism of Aub and DuBois⁸ is used. Since only the general outlines are discussed here, the statements are applicable as well to the standards of Harris and Benedict.⁷ The rise indicated in the metabolism curve at puberty is not spoken of because it is the source of some difference of opinion on which the data can shed no light.

Superficially, the changes in pulse rate with age are similar to the changes in the metabolic rate with age. Both curves are high in infancy as compared with adult life. The resemblance would be even greater if the age-curve of metabolism prepared by Benedict⁴⁵ were used, since the highest point is more narrow and is placed at an earlier age, between

45 Benedict, F G Energy Requirements of Children from Birth to Puberty, Boston M & S J 181 107-139 (July 31) 1919

1 and 2 years In the two sexes there is a difference of 10 per cent in basal pulse rate (about 71 beats per minute) and of 7 per cent in basal metabolic rate

On short examination, however, a number of differences are seen. The pulse is high in infancy while the metabolism is as low as that of adults. This discrepancy is even more marked in the premature infants studied by Talbot, Sisson and Moriarty,¹⁷ in which the metabolism was exceptionally low while the pulse rate was even higher than that of the fetus. In adults the pulse rate remains the same, while metabolic rate drops at a slow but constant rate through life. In regard to sex differences, while the amount of difference in pulse rate and metabolism is

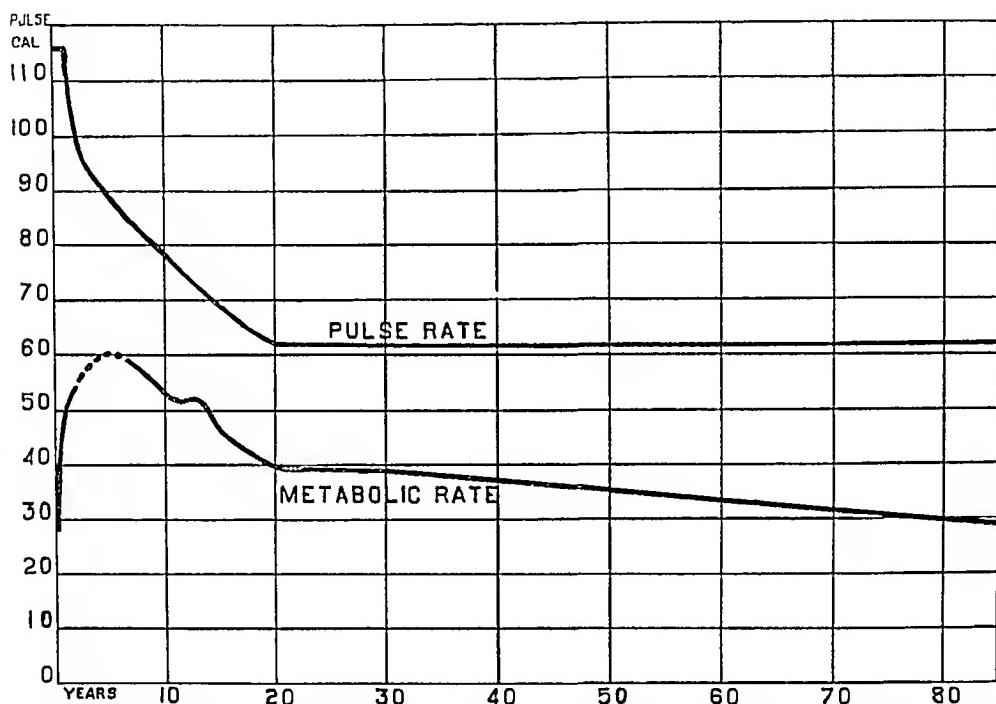


Chart 5—Curve of basal pulse rate for males, aged from 1 to 80 years, from Charts 1 and 2, above, compared to the curve of basal metabolism per square meter of body surface hourly for males, from Aub and DuBois

numerically similar, males with lower pulse rate have higher metabolism and women with higher pulse rate have lower metabolism. This is contrary to the changes in subjects in whom the higher pulse rate is associated with metabolism also high.

This discussion is based on 736 observations made under the strict basal conditions used in experimental work by well known observers. The curve for males includes 361 observations, the curve for females, 375. As has already been mentioned, not all age groups are equally well represented. In making the average for adult males, 146 observations were used, for adult females, 85 observations were used. The average rate at one year was based on 62 and 58 observations, respectively, for males and females.

We believe that a knowledge of the basal pulse rate and the normal variations at all ages is of importance to the increasing number who make and interpret basal metabolism determinations. Evidence is accumulating that the pulse rate is a rough guide to the metabolism. A number of the persons visited by a physician were resting in bed, and had taken no food for a number of hours. Under these circumstances, a comparison of the pulse rate to the average found under basal conditions is more accurate than comparison to the old values determined under conditions of partial rest.

CONCLUSIONS

- 1 The average basal pulse rate, in adults aged from 20 to 40 years, is 62 for males and 69 for females.
- 2 The average basal pulse rate at 1 year is 116 for males and 122 for females.
- 3 The curve of average basal pulse rate drops rapidly for the first three years of life, then less rapidly to the adult level reached at 20 years of age.
- 4 The variability of the pulse rate under basal conditions is greater in children than in adults, and greater in females than in males.
- 5 The average basal pulse rate of females is greater than that of males at all age periods after 10 years in the data assembled here. It varies from 4 to 11, with an average of 7 beats a minute.

THE SUGAR CONTENT OF THE CEREBROSPINAL FLUID AND ITS RELATION TO THE BLOOD SUGAR *

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During the last four years, the prevalence of encephalitis with its attendant diagnostic difficulties has brought out the importance of the quantitative determination of sugar in the spinal fluid. Kraus and Pardee¹ state that they found this the one finding of any positive value in a large percentage of spinal fluids from encephalitic patients. Because of the stress laid on this point in the literature, we started making routine sugar determinations on the spinal fluids in all cases in which the possibility of encephalitis was considered (Table 2), but we soon found that we had no way of knowing whether the figure obtained for the sugar content of the spinal fluid was normal. The literature gave us no help because of the great variation in the figures given for the normal sugar content in spinal fluid.

We therefore undertook a study of the sugar content of the cerebrospinal fluid with particular attention to the following points:

1 Does the sugar content of the cerebrospinal fluid remain constant in the same individual?

2 Is there a level which, within reasonable limits, might be considered normal for different individuals?

3 Is there any relation between the sugar content of the cerebrospinal fluid and that of the blood and, if so, is this relationship constant?

4 What influence has the ingestion of carbohydrates on the sugar content of the cerebrospinal fluid, and on the relation between the sugar content of the cerebrospinal fluid and the blood?

5 If there is a definite relation between the sugar content of the cerebrospinal fluid and the blood, what variations from this relation are found in pathologic conditions of the central nervous system, and can these changes be attributed to any definite causes?

In our work, the figures are given in milligrams per hundred cubic centimeters of cerebrospinal fluid or blood, as determined by the Benedict colorimetric method.

* From St Luke's Hospital

1 Kraus, W M, and Pardee, I H Arch Neurol & Psychiat 5 710 (June) 1921, Acute Epidemic Encephalitis, Tr A Research in Nervous and Mental Diseases, 1921, p 99

1 INDIVIDUAL VARIATIONS IN THE SUGAR CONTENT OF THE CEREBROSPINAL FLUID

Our results would indicate that the sugar content of the cerebrospinal fluid is not constant in the same individual. As shown by the tables, estimations made on successive mornings after a night's fasting showed variations of from 4 to 16 mg.

2 SUGAR CONTENT LEVEL OF THE CEREBROSPINAL FLUID IN DIFFERENT INDIVIDUALS

Most investigators have assumed that there is a level of sugar content of the cerebrospinal fluid which, within reasonable limits, might be considered normal. That there is some error in this assumption is indicated by the great variation in the conclusions of different investigators as to the normal figure, and also by the wide variation of the normal figures given by each of several persons. Nawratzki² (1897) considered 46 mg per hundred cubic centimeters of spinal fluid as normal. In 1909, von Jaksch reported twenty cases with the sugar content of the cerebrospinal fluids ranging between 60 and 80 mg per hundred cubic centimeters of spinal fluid. In 1912, Mestrezat³ concluded that the normal level varied between 48 and 53, and, in 1920, Marie and Mestrezat⁴ showed that their idea was unchanged. In 1913, Kopetsky⁵ reported eight cases with an average of 46. In 1915, Hopkins⁶ using the modified Bang's micromethod, concluded that the normal level was between 60 and 75. In 1921, Coope⁷ reported the sugar content of the cerebrospinal fluid of three normal people at 64, 69 and 83. He did not state the time of taking the fluid. In 1921, Foster,⁸ using the Folin-Wu method, reported the variation in twenty-two normal spinal fluids as lying between 44.2 and 61.4, with an average of 52.8. In 1923, Kelley⁹ concluded from a study of the sugar content of the spinal fluids in 1,000 cases that the sugar content of normal spinal fluid lies between 40 and 95 mg per hundred cubic centimeters of cerebrospinal fluid. He makes no statements as to the time at which the spinal fluids were taken, or as to the relation to the blood sugar.

2 Nawratzki Zur Kenntniss der Cerebrospinal flüssigkeit, Ztschr f physiol Chem, 1897, p 533

3 Mestrezat J de physiol et de pathol gen, Paris, 14 504, 1912

4 Marie, P., and Mestrezat Bull de l'Acad de med, Paris, 83 103 (Feb 3) 1920

5 Kopetsky Ztschr f Ohrenh 68 1-19, 1913

6 Hopkins Am J M Sc 150 847 (Dec) 1915

7 Coope, R Quart J Med 15 1 (Oct) 1921

8 Foster, H E Hyperglycorachia in Encephalitis, J A M A 76 1300 (May 7) 1921

9 Kelley, A G Serology of Spinal Fluid and Blood in Encephalitis, Southern M J 16 407 (June 23) 1923

Our figures indicate that there is no normal level for the sugar content of the cerebrospinal fluid, except within very wide limits. In the ordinary cases, the figures varied from 40 to 77 mg per hundred cubic centimeters of cerebrospinal fluid. In disturbances of the central nervous system (Table 4), the sugar content varied from 47 to 105 mg per hundred cubic centimeters. Cases of cerebrospinal syphilis (Table 5) showed variations of from 38 to 74 mg per hundred cubic centimeters. In the diabetic cases with no pathologic condition of the central nervous system, the figures ranged from 80 to 200 mg per hundred cubic centimeters (Table 7).

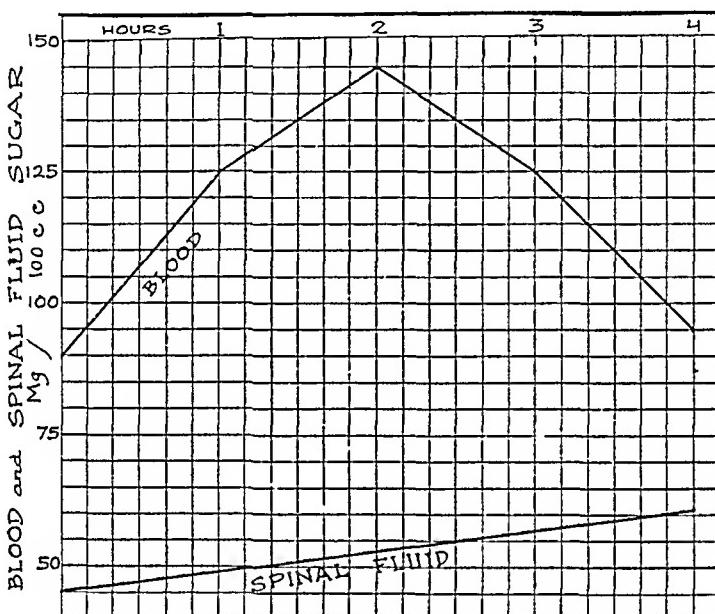


Chart 1—Blood and spinal fluid sugars before and after breakfast

³ RELATION BETWEEN THE SUGAR CONTENT OF THE CEREBRO-SPINAL FLUID AND THE SUGAR CONTENT OF THE BLOOD

Notwithstanding this wide variation in the sugar content of the cerebrospinal fluid, the charts appear to show a definite relation between the cerebrospinal sugar and the blood sugar. But few investigators have suggested a definite relationship between the blood sugar and the cerebrospinal fluid sugar. Hopkins⁶ appears to have been one of the first, if not the first, to notice that there was some relation between the sugar content of the cerebrospinal fluid and of the blood. Using the modified Bang's micromethod, he concluded that the normal spinal fluid sugar level was between 60 and 75. Although his figures varied so greatly that his idea was far from proved, he concluded that the normal spinal fluid sugar was approximately 10 mg less than the blood sugar. Neuberg stated that the spinal fluid sugar was the same as that of the blood. In 1916, Weston, using the method of Myers and Bailey, found

in a series of experiments that the cerebrospinal fluid sugars varied from 60 to 70, with the blood sugars in the same cases varying between 100 and 120. The relative times of taking the cerebrospinal fluid and the blood were not stated however.

The more recent figures in the literature disagree entirely with the conclusions of Hopkins and Neuberg. From the figures given by Thalheimer and Updegraff¹⁰ (1922) in reporting the spinal fluid sugars and the blood sugars of six normal cases, we find the results given in Table 1. Both spinal fluid and blood were taken before break-

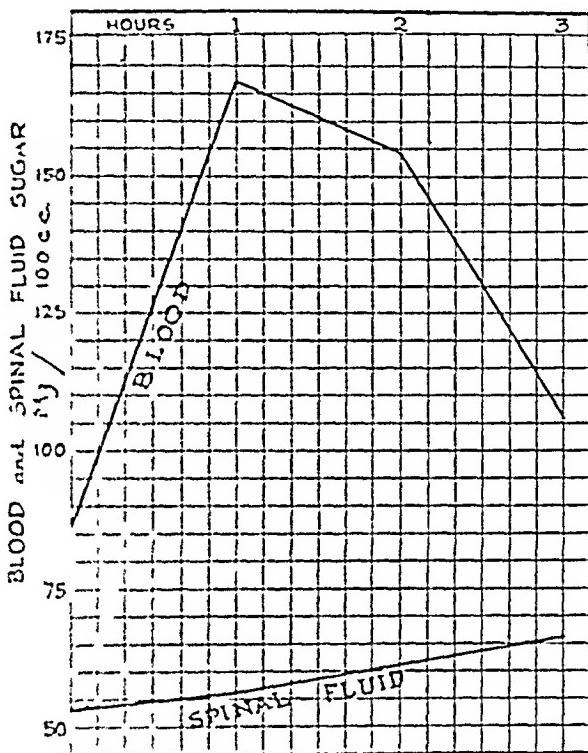


Chart 2—Blood and spinal fluid sugars before and after glucose tolerance tests

fast, after a night's fasting. These cases show a fairly constant per cental relation between the sugar content of the spinal fluid and of the blood, the average figure being 46 per cent. This finding agrees with the conclusion of Wilcox and Lytle¹¹ (1923) that the normal cerebrospinal fluid sugar is, with some variation, half that of the blood sugar.

Palonavski and Duhot¹² (1923) showed a definite relation between the sugar content of the cerebrospinal fluid and of the blood. By their method of determination of blood sugars, the blood sugars, in a series

¹⁰ Thalheimer, W., and Updegraff, H. Comparison of Several Clinical Quantitative Blood Sugar Methods, *Arch Neurol & Psychiat* 8 15 (July) 1922

¹¹ Wilcox, H. B., and Lytle, J. D. *Arch Pediat* 40 215 (April 23) 1923

¹² Palonavski, M., and Duhot, E. *Presse med* 31 60 (Jan 20) 1923

TABLE 1—*Spinal Fluid Sugars and Blood Sugars in Six Normal Cases (Thalheimer and Updegraff)*

Case	Blood Sugar	Spinal Fluid Sugar	Percental Relation
			Spinal Fluid Sugar to Blood Sugar
1	185	55	40.7
2	158	74	46.4
3	129	63	48.8
4		64	
5	115	53	46.0
6	117	56	47.8

TABLE 2—*Spinal Fluid Sugars*

No	Age	Diagnosis	Date	Spinal Fluid			Wassermann	Sugar	Remarks
				Total	Cells	Globulin			
1	59	Encephalitis	3/30/23			2	+	0	71 Necropsy, many cerebral hemorrhages
			4/7/23			2	0	0	74
			4/11/23	11	4	7	0	0	58
			4/19/23	22	3	19	+	0	53
2	11	Encephalitis				4	0	0	74
3	26	Encephalitis	2/14/23	30	4	26	+	0	53
			2/21/23	27	2	25	+	0	53
4	30	Encephalitis	1/4/23	43	2	41	0	0	67
			1/5/23	18	2	17	0	0	61
			3/11/23			7	++	0	60
			3/12/23			4	0	0	63
5	30	Encephalitis (striae and psychic type)	1/23/23			15	0	0	80
			1/27/23			14	0	0	95
6	31	Postencephalitic asthenia				5	+	0	50
7	13 mos	Tuberculous meningitis	9/14/23	60	10	90	++++	0	Too small to estimate
8	36	Tuberculous meningitis?	8/28/23	195	127	68	++	0	57 Positive in guinea pig, December 1, patient alive, up and about
			8/30/23	111	11	100	+++	0	46
			9/2/23	195			+	0	57
9	60	Paehymeningitis internal hemorrhagia	3/15/23	9	1	4	0	0	71 Necropsy (Red blood cells 3)
10	10	Poliomyleitis, facial paralysis	8/17/23	13	2	11	++	0	40
			8/20/23	16	4	12	++	0	24
			7	1	6	++	0	48	After serum
11	39	Carcinoma of bronchus with edema of brain	10/10/23			5	+	0	70 Spinal fluid bloody
			10/17/23	530			+++	0	20 After serum (necropsy)
12	13 mos	Acute ileocolitis (encephalitis?)	9/16/23			5	0	0	50
			9/23/23			1	0	0	53
13	9	Infected left ventricle				47	0	0	44
14	16	Epilepsy				4	+	0	62
15	50	Chronic tonsillar and oral sepsis				4	0	0	40
16	40	Malta fever		5	1	4	0	0	43
17	41	Syringomyelia		13	6	7	0	0	50 Blood in spinal fluid
18	23	Malignant endocarditis (staphylococcus), with hemiplegia	2/8/23	268	236	32	+	0	63 Necropsy
19	53	Cerebrospinal syphilis with optic atrophy (treated)	1/15/23	490	302	88	+++	0	42 Spinal fluid contained hemolyzed blood On 10/12/24 blood Wassermann reaction was +++ and spinal fluid Wassermann 0

* In this and the following tables, P, under cells, indicates polymorphonuclears, and L lymphocytes

of ordinary cases, ranged from 52 to 88, which was uniformly slightly higher than the spinal fluid sugars which ranged from 45 to 85. The administration of epinephrin to patients giving a hyperglycemia produced a rise in the spinal fluid sugar, which did not return to normal until after the blood sugar had returned to normal. They concluded that the relation between the spinal fluid sugar and the blood sugar was important, but that the spinal fluid figure alone was not of value.

Our figures in Table 9 would indicate that the findings of Thalheimer and Updegraff,¹⁰ which are borne out by Wilcox and Lytle,¹¹ are essentially correct. The percental relation of spinal fluid sugar to blood sugar in the sixteen determinations in the ordinary cases falls

TABLE 3.—*Spinal Fluid and Blood Sugars in Ordinary Cases*

No	Age	Diagnosis	Spinal Fluid				Blood Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar	Remarks
			Cells L	Glob- ulin	Wasser- mann	Sugar			
1	67	Arteriosclerosis	1	0	0	49	105	47	
2	51	Bronchial asthma, chronic cardiovascular disease	1	0	0	43	88	49	
3	70	Chronic cardiovascular disease	2	±	0	62	118	52	
4	30	Cardiac hypertrophy and decompensation	2	+	0	55	100	55	
5	25	Chronic cardiovascular disease	6	0	0	57	100	57	
6	61	Cancer of the stomach	4	+	0	52	105	50	
7	65	Cancer of sigmoid	3	0	0	55	105	52	
8	49	Colitis	6	+	0	40	86	46	
9	48	Duodenal ulcer	1	+	0	77	118	65	
10	53	Hypertension, chronic nephritis	1	+	0	67	105	63	
11	35	Hypoglycemia	1	+	0	48	84	57	
12	22	Chronic polyarthritis				50	100	50	
13	36	Tuberculosis of lungs and spine, tertiary syphilis	1	0	0	48	95	50	Blood Wassermann ++++
14	52	Duodenal ulcer	5	+ Anticomplementary, probably negative	54	95	57		
15	16	Iobar pneumonia	1	0	0	51	110	46	

within the limits of 45 and 65 per cent, giving an average figure of 53 per cent. Of the eight determinations in the treated cerebrospinal syphilis cases, all but one lie between 45 and 65 per cent, giving an average of 55 per cent. The six determinations in the diabetic cases also fall between 45 and 65 per cent, with an average figure of 55 per cent. Of the twelve determinations in ordinary diseases of the central nervous system (Table 4), only one lies below 45 and two above 65 per cent, giving an average figure of 57.7 per cent. We find, therefore, that, in a total of forty-two determinations, only one lies below and three above the limits of 45 and 65 per cent, the average being 54.8 per cent. This constant percental relation is found notwithstanding the great variation in the sugar content of the cerebrospinal fluid and of the blood, as expressed in milligrams per hundred cubic centimeters.

These figures would indicate that there is a definite relationship between the cerebrospinal fluid sugar and the blood sugar, and that the figure representing this relationship, stated as the percental relationship between the two, is relatively constant, lying between 45 and 65 per cent. This may be considered a reasonable variation, provided determinations are made on both blood and cerebrospinal fluid taken at the same time, after a night's fasting.

4 INFLUENCE OF THE INGESTION OF CARBOHYDRATES ON THE SUGAR OF THE CEREBROSPINAL FLUID AND ITS RELATION TO THE BLOOD SUGAR

In 1920, Isamu Ino¹³ worked out carefully in rabbits the effect of the carbohydrate intake on the sugar content of the cerebrospinal fluid.

TABLE 4.—*Pathologic Conditions of the Central Nervous System Without Change of Relation of Cerebrospinal and Blood Sugar Content*

No	Age	Diagnosis	Spinal Fluid				Percental Relation		Remarks
			Cells 1 L	Glob ulin 0	Was- ser- mann 0	Blood Sugar 47	Blood Sugar 100	Spinal Fluid Sugar to Blood Sugar 47	
1	53	Cancer of stomach with hemorrhage into floor of 4th ventricle							Necropsy
2	70	Hemiplegia, cerebral thrombosis	2 L	+	0	52	100	52	
3	43	Hemiplegia	P 13, L 17 30 6	+	0	57	100	57	Fluid contained hemolyzed blood
			P 2, L 4 4 L	+	0	53	87	61	Fluid yellow
4	19	Manic depressive psychosis		0	0	50	80	62	
5	40	Unexplained headaches chronic malaria	1 L	0	0	57	83	69	
6	28	Alcoholic neuritis	5 L	++	0	57	83	69	
7	64	Urticaria, uremia	2 L	0	0	74	118	62	(In delirium)
						64	118	53	(Normal)
8	72	Uremia, aurie fibrillation	5 L	0	0	83	188	44	No glycosuria
9	59	Uremia, aurie fibrillation	P 6, L 1	+	0	67	105	63	Spinal fluid bloody
10		Uremia, chronic glomerular nephritis, hypertension	P 5, L 1 1 L	0	0	105	200	52	No glycosuria

and the relation between the changes resulting and the changes in the blood sugar. In his work, the blood sugar reached its highest point immediately after the intravenous injection of the carbohydrate—1 gm of glucose, galactose or lactose per kilogram of body weight—returning to normal within an hour. The spinal fluid sugar did not reach its maximum until one hour after the injection, and then required four hours to return to normal.

Due to the impracticability of doing any great number of lumbar punctures on any one patient, we were unable to obtain any curves of

13 Ino, Isamu. *Acta Scholae Medicinalis, Univ Kioto*, No 4, March 25, 1920-1923, p 609

great length, but the changes we observed in our work did not take place as rapidly and were not as great as those obtained by Ino in his work on rabbits. This is probably explained by the fact that, in his work with rabbits, Ino took the cerebrospinal fluid from the base of the skull. Any changes due to fluid of a different composition coming from the choroid plexus should register more quickly there than in the fluid obtained from the lumbar region in man, both because of the lesser distance of flow and the smaller quantity of the original spinal fluid by which it would be diluted.

In our work, blood and cerebrospinal fluid were taken at the same time after the patient had fasted over night. An ordinary hospital

TABLE 5.—*Pathologic Conditions of the Central Nervous System in Which Changes Have Been Reported in the Cerebrospinal Fluid Sugar*

No	Age	Diagnosis	Date	Spinal Fluid				Blood Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar	Remarks
				Cells	Glob ulin	Wns mann	Sugar			
1	29	Encephalitis	11/18/23	S L	++	0	54	96	56	Two days before rash
			11/28/23	I I	++	0	70	105	66	
			12/10/23	P 5 L 6	++	0	56	105	53	
			12/19/23	I I L	++	0	54	105	53	
2	70	Herpes zoster, diabetes mellitus	11/17/23	2 L	0	0	55	176	31	Three weeks after rash
			12/17/23	3 I	0	0	95	185	51	
3	65	Ventricular purulent leptomeningitis from sinuses		2 I	0	0	63	100	63	Spinal fluid sugar 3 hours after break fast, blood sugar fasting, necropsy
4	37	Pulmonary tuberculosis, tuberculous meningitis	12/7/23	S 1 J 79, P 6	+++	0	Too small to estimate	134	Blood Wassermann reaction, cholesterol sterilized antigen 4+, acetone insoluble antigen 0	
			12/8/23	L 73, P 17	++	0	15	143	10	
										Repeated blood Wassermann reaction, cholesterol sterilized antigen 4+, acetone insoluble antigen 0, necropsy
5	52	Diabetes, thrombosis of lateral sinus with pneumococcus Type III, blood culture		1 L 2 L	0 0	0	134 84	236 200	56 42	Before At height of symptoms

breakfast or the routine glucose test of 15 gm of glucose per kilogram of body weight was given the patient, and the blood and spinal fluids taken simultaneously before and at different periods afterward, as indicated in Table 8.

In every case, there was a small but definite rise in the cerebrospinal fluid sugar content. This varied from 7 to 16 mg in the five cases. The rise in blood sugar was temporary only, so that cerebrospinal fluid with an increased sugar content would be "secreted" only during that period. This would then be diluted by the fluid already present, and the rise as noted in the fluid from the lumbar region would not only be decreased by this dilution, but also would appear later than the rise in the blood

sugar content, as the fluid with the higher sugar content must flow or diffuse down to the lumbar region

In our five cases, the rise is small as compared to the rise in the blood sugar, but it is constant and definite. As in the case of Ino's rabbits, the maximum rise occurs some time after the maximum rise in the blood sugar. In the one case which we ran for six hours, the maximum rise was reached at the end of four hours with the return to normal at the end of six hours.

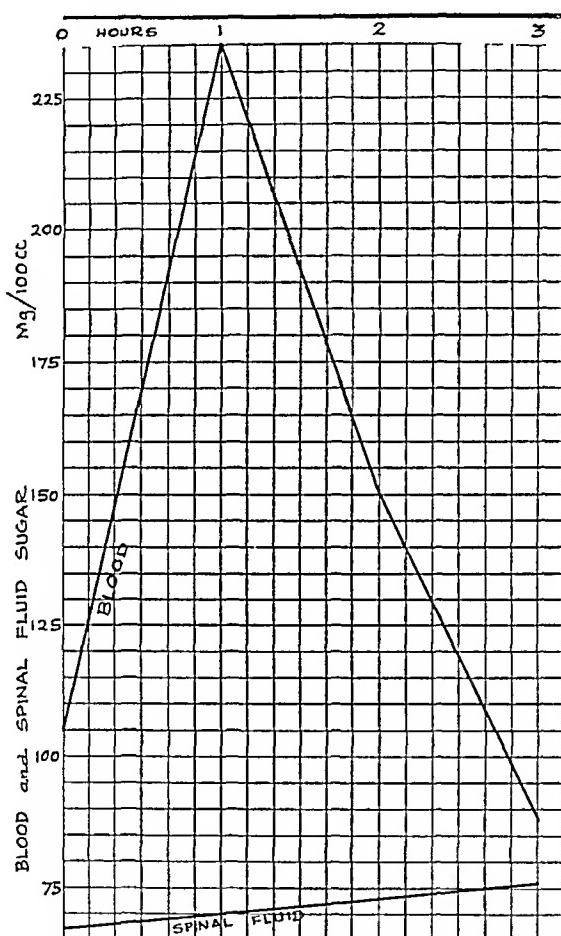


Chart 3—Blood and spinal fluid sugars before and after glucose tolerance tests

The extent to which the relation of cerebrospinal fluid sugar to blood sugar is disturbed by the ingestion of carbohydrate is shown by the figures in Table 8. The percentages, instead of lying between 45 and 65, range from 33 to 82. That this is due both to an early rise in the blood sugar and a late rise in cerebrospinal fluid sugar is shown by the fact that the range is both lower and higher than the fasting relationship. The fact that the percental relationship between the cerebrospinal fluid sugar and the blood sugar is thrown off by food intake

demonstrates the necessity of making these determinations at the same time after a night's fasting. Determinations made at other times are of no value.

5 VARIATION OF PERCENTAL RELATIONSHIP IN PATHOLOGIC CONDITIONS OF THE CENTRAL NERVOUS SYSTEM

The literature contains many reports of the sugar content of the cerebrospinal fluid in pathologic cases. With a few exceptions, these appear to have but little value, and in most of these cases no attempt is made to show whether or not the blood sugar was normal. In only one instance were uniform conditions used in taking the blood and spinal fluid.

TABLE 6.—*Spinal Fluid and Blood Sugars in Cerebrospinal Syphilis*

No	Age	Diagnosis	Spinal Fluid				Percental Relation		Remarks	
			Cells	Glob- ulin	Was ser- mann	Blood Sugar	Blood Sugar	Spinal Fluid Sugar to Blood Sugar		
1	28	Cerebrospinal syphilis untreated, gastro crisis	80	++	C * A-I	+++ +++	88	110	33	Blood Wassermann reaction +++
2	56	Cerebrospinal syphilis, tabs treated	3	+	0	48	95	50		
3	47	Cerebrospinal syphilis, tabs treated	3	+	C A-I	+++ 0	58	108	53	Blood Wassermann reaction 0, in 1918 +++
4	66	Cerebrospinal syphilis, tabs treated	10	++	Anticompli- mentary	55	90	61	Blood Wassermann reaction +++	
5	72	Cerebrospinal syphilis, tabs treated	6	0	0	74	100	74		
6	60	Tertiary syphilis, transitory aphasia and hemiplegia, treated	1	0	0	54	100	54	Blood Wassermann reaction 0, in 1914 was 4+	
7		Congenital syphilis, treated 6 years	3	0	0	48	95	50	Blood Wassermann reaction 0, in 1917 was 4+	
8		General paralysis, treated	1	++	0	53	105	50		

* C indicates cholesterolized antigen, A I, acetone insoluble antigen.

It has been definitely shown that, in meningitis due to tuberculosis, staphylococcus or meningococcus, there is nearly always an actual fall in the cerebrospinal fluid sugar. In 1895, Quincke¹⁴ reported that the reducing substances in the spinal fluid may disappear in meningitis. Articles by Coope,⁷ Thalheimer and Updegraff,¹⁰ and Wilcox and Lytle¹¹ contain typical figures for meningococcus, staphylococcus and tuberculous meningitis cases. In the two latter articles, the authors showed that this decrease was unaccompanied by a decrease in the blood sugar, demonstrating that there is an actual fall in the percental relation of the sugar content of the blood and of the cerebrospinal fluid. The

14 Quincke Ueber Lumbal punktion, Berl klin Wchnschr, 1895, No 41

fall in the sugar content of the cerebrospinal fluid and the fall in the percental relation of the sugar contents of the blood and of the cerebrospinal fluid are noted in Case 7 of Table 2 and in Case 4 of Table 5. Case 8 of Table 2 was probably a mistake in diagnosis as the subsequent course of the case would make the diagnosis of anterior poliomyelitis much more probable, although injection into a guinea-pig resulted in positive tuberculous lesions. The spinal fluid sugar findings bear this out.

It is interesting to note that the cerebrospinal fluid sugar was lowered by the injection of antimeeningococcus serum (Table 2). This was probably due to dilution, although Ino,¹³ in a series of experiments on human cerebrospinal fluid, in test tubes and in rabbits, showed that the reduction of spinal fluid sugar was proportionate to the number of white blood cells per cubic millimeter, and that all bacteria excited more

TABLE 7.—*Spinal Fluid and Blood Sugars in Diabetic Patients*

No	Age	Diagnosis	Spinal Fluid				Blood Sugar	Per cental Relation Spinal Fluid Sugar to Blood Sugar	Remarks
			Cells L	Glob uin	Was sei mann	Blood Sugar			
1	66	Diabetes, chronic nephritis	2	0	0	Lost	238		
						103	182	56	
2	51	Diabetes, cholecystitis, pancreatitis	1	0	0	200	315	60	
3	45	Diabetes, tertiary syphilis	1	0	0	93	170	54	Blood Wassermann reaction +++
4	52	Diabetes	1	0	0	134	238	56	
5	51	Diabetes mellitus	2	0	0	80	154	52	
6	70	Diabetes mellitus	2	0	0	95	185	51	

or less decomposition of the sugar in vitro, but not in proportion to the number of bacteria per cubic centimeter. He also showed that, in rabbits, the spinal fluid sugar was not reduced by starvation unless the rabbits were in a weakened condition.

In work with other cases, these investigators found no important lowering of the cerebrospinal fluid sugar, except in one type of cases. In 1923, Kelley⁹ reported an average sugar content of the spinal fluid of 21 mg per hundred cubic centimeters in 195 untreated cases of syphilis of the central nervous system, after treatment, in 100 cases, the average was 62. Our one case of untreated cerebrospinal syphilis gives a low figure and low percentage, agreeing with the figures of Kelley. The treated cases fall within normal limits.

Epidemic encephalitis is the disease in which the greatest amount of work has been done on the changes in cerebrospinal fluid sugar. In 1920, Dopter¹⁵ reported a case with a cerebrospinal fluid sugar of 85,

from which he concluded that the high sugar content was of diagnostic importance in differentiating the disease from acute or tuberculous meningitis, but that it was not pathognomonic nor even a constant finding in encephalitis lethargica.

In 1920, Netter¹⁶ reported six cases with cerebrospinal fluid sugar figures varying from 70 to 97, with an average of 86. In 1920, Laporte and Rouzaud¹⁷ reported twelve cases in which the cerebrospinal fluid

TABLE 8.—Blood and Spinal Fluid Sugar Content After Ingestion of Glucose or Food

No	Age	Diagnosis	Spinal Fluid				Percental Relation Spinal Fluid Sugar to Blood Sugar	Remarks
			Cells	Glob	Was ser munn	Blood Sugar		
1	70	Cardiac hypertrophy and decompensation	2 L	0	15	90 125 140 125 95	50	Fasting One hour after breakfast Two hours Three hours Four hours
2	43	Hemiplegia	P 1 ^a , L 17 P 2, L 4	0 6 0 56	0 0 63 87 167	Fluid contained hemolyzed blood (Fluid yellow)	61 33	Fasting One hour after glucose test Two hours Three hours Four hours
3	73	Hypertension chronic nephritis	1 L	+	0 66 67 105 235	150 154 111 60	64	Fasting One hour after glucose Two hours Three hours Four hours
4	79	Mental depressive psychosis	4 L	0 56	0 50 56	76 80 150 59	85 62 37 82	Fasting One hour after glucose Two hours Three hours Four hours
5	47	Cerebrospinal syphilis (treated 7 years)	3 L	+	± 51 51 57	105 100 105 90 100	48 48 63 50	Fasting One hour after glucose Two hours Four hours Six hours

sugar varied from 66 to 101, giving an average of 88. Coope⁷ found ninety-two cases reported in the literature of 1920, in which only seventeen, or 18 per cent, showed figures of 55, or less. The variations were as follows: Seven cases showing from 100 to 110 mg of sugar per hundred cubic centimeters of spinal fluid, thirteen cases showing from 90 to 99 mg, twenty-five cases showing from 80 to 89, twenty, from 70 to 79, eight, from 60 to 69, twelve, from 50 to 59, six, from 40 to 49, and one from 30 to 39.

In 1921, Foster⁸ reported eleven cases of encephalitis lethargica, in six of which blood sugar estimations were made. The relative time of

16 Netter, A. Bull et mém Soc med d hôp de Paris **44** 441 (March 26) 1920.

17 Laporte and Rouzaud. Bull et mem Soc méd d hôp de Paris **44** 422 (March 19) 1920.

taking the blood and the cerebrospinal fluid was not stated. Using the Folin-Wu method, the cerebrospinal fluid sugars varied from 53.5 to 113, and the blood sugars from 70 to 100. Of these spinal fluid sugars, only one came within the limits found in the sugar content of twenty-two normal spinal fluids, although the blood sugars lay within the normal limits.

In 1921, Kraus and Pardee¹ reported twelve cases of encephalitis lethargica with cerebrospinal fluid sugars varying from 62 to 95. Of these cases, all but two had blood sugars below 120, in these two cases, the blood sugars were 143 and 190. These investigators thought that

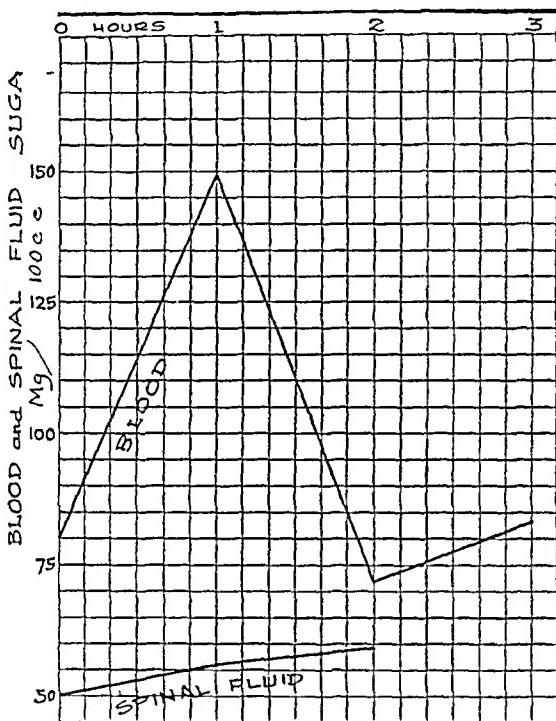


Chart 4.—Blood and spinal fluid sugars before and after glucose tolerance tests.

encephalitis caused vascular lesions which made the walls more permeable to sugar. In the same year, Coope⁷ reported eleven cases of encephalitis lethargica, with spinal fluid sugars varying from 54 to 94, the average being 74.

Hirsch¹⁸ (1921) thought that the high spinal fluid sugar might be due to hyperglycemia, since the intravenous injection of bacteria in animal experimentation gave a hyperglycemia. He also stated that acute infectious diseases caused a hyperglycemia. This would be indicated by the cases reported by Thalheimer and Updegraff¹⁰ (Table 10), as the percental relation between the spinal fluid sugar and the blood sugar is

TABLE 9.—Percental Relation of Spinal Fluid Sugar to Blood Sugar in All Cases Studied

Case	Number of Determinations Made	Average Relation, per Cent	Number of Cases with Relation		
			44 per Cent	45-55 per Cent	56-65 per Cent
Ordinary	16	51	0	11	5
Pathologic conditions of central nervous system without change in relation	12	57.7	1	4	5
Treated central nervous system syphilis	8	55	0	6	1
Diabetes	6	55	0	3	1
Total	42	51.8	1	24	14
					3

TABLE 10.—Results Obtained by Thalheimer and Updegraff in Work on Encephalitis Cases*

Number	Time Taken	Blood Sugar	Spinal Fluid Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar
1	After breakfast		161	
	Before breakfast	297	177	57
2	After breakfast	182	126	69
	Before breakfast	196	134	68
	Before breakfast	208	117	56
	Before breakfast	150	71	47
3	Before breakfast	174	89	51
	Before breakfast	144	82	57
4	Two hours postmortem		79	
5	Four hours after breakfast	188	90	48
6	Before breakfast	159	80	50
7	Before breakfast	155	93	60
		163	84	51
8	Two hours postmortem	226	125	55
9	Three hours after lunch	211	80	38
10	Before breakfast	148	84	57
11	Before breakfast	173	85.4	47
	Before breakfast	179		
	Before breakfast	139		
12	Before breakfast	115	56	48
13	One hour after lunch		82	
14	Five hours antemortem		136	

* Since, according to our findings, the relation between the cerebrospinal fluid sugar and the blood sugar is thrown off by the ingestion of food, only those determinations made on the fluid and blood taken before breakfast are of value. The figures stating percental relation were added by us.

TABLE 11.—Results Obtained by Wilcox and Lytle in Work on Encephalitis Cases

Number	Age	Blood Sugar	Spinal Fluid Sugar	Percental Relation Spinal Fluid Sugar to Blood Sugar
1	7	93	111	61
		111	57	46
2	7	102	51	96
			98	85 ?
			87	77 ?
			79	
3	11	143	121	71
		101	66	65
4	11	125	89	71
		95	71	74

practically undisturbed. In contrast to this, Wilcox and Lytle¹¹ found the cerebrospinal fluid sugar high in relation to the blood sugar in practically all their cases, although the relative time of taking the spinal fluid and the blood was not stated (Table 11).

In the one case of encephalitis which we have had since we began to work out the relation of the cerebrospinal fluid sugar to the blood sugar, the percental relation fell within the expected limits. Some of the other cases (Table 2) gave high figures for the sugar content of

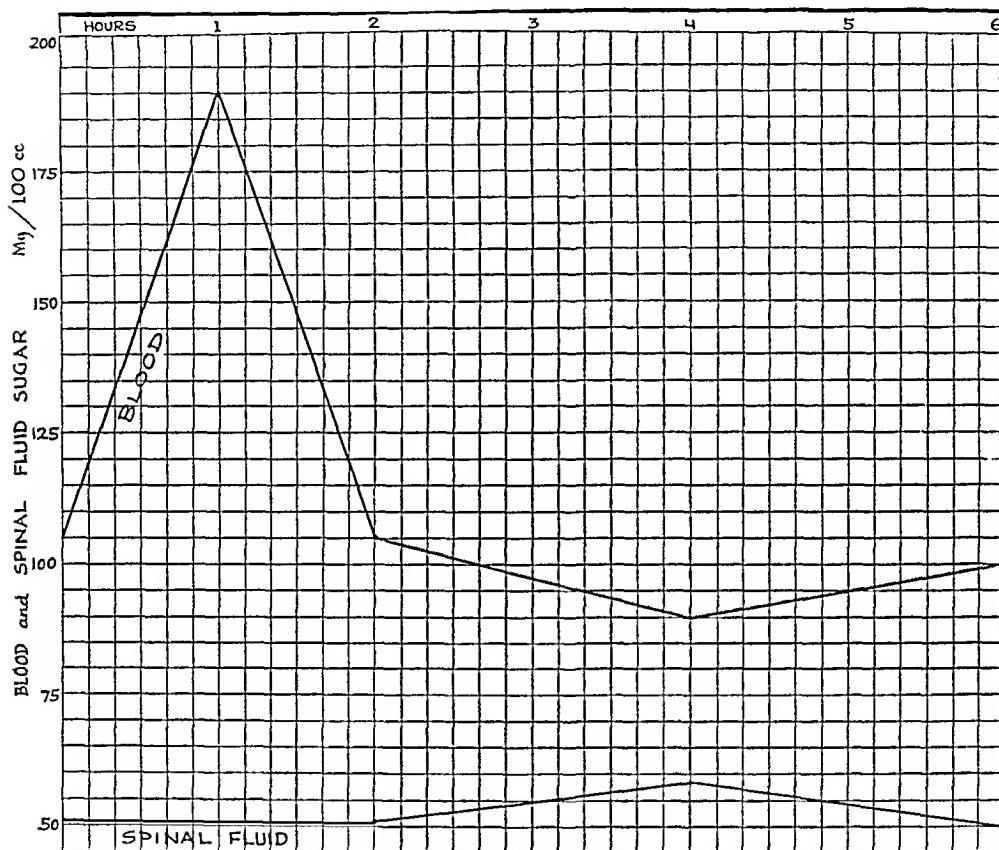


Chart 5—Blood and spinal fluid sugars before and after glucose tolerance tests.

the cerebrospinal fluid, but the relation to the blood sugar was not determined.

High spinal fluid sugars have been reported in several other conditions. In 1920, Fiessinger and Janet¹⁹ reported three cases, one of diffuse sarcomatosis with sarcoma in the basilar process of the sphenoid pressing on the mesencephalon, with sugar contents of the spinal fluid of 103 and 293, one of meningeal hemorrhage, with sugar contents of the spinal fluid of 95 and 115, which is about that of normal blood, due

19 Fiessinger, N., and Janet Bull et mem Soc med d hôp de Paris 45 145, 1920

to the amount of blood in the fluid from the hemorrhage, and one of terminal meningeal miliary tubercles (not tuberculous meningitis) with sugar content of the spinal fluid, 180, without glycosuria. In 1912, Achard and Rouillard²⁰ reported a case of mesencephalic syphilis simulating encephalitis with cerebrospinal sugar of 75 and 70.

A number of cases of brain tumor with high cerebrospinal fluid sugar have been reported in recent literature. In 1922, Thalheimer and Updegraff¹⁰ reported such a case with a cerebrospinal fluid sugar content of 179. In 1923, Wilcox and Lytle¹¹ reported a case of glioma of the cerebellum with a blood sugar of 93 and a cerebrospinal fluid sugar of 93.

CONCLUSIONS

To be of value in determining whether or not a spinal fluid sugar is high or low, the fluid must be taken after a night's fasting and the sugar content compared to that of the blood taken at the same time.

Our figures would indicate that the following conclusions might be drawn:

1. The sugar content of the cerebrospinal fluid is not constant in the same individual.

2. There is no level, within reasonable limits, which might be considered normal for different individuals.

3. There is a definite relationship between the sugar content of the cerebrospinal fluid and of the blood, which may be expressed as the per cental relation of the sugar content of the cerebrospinal fluid to the sugar content of the blood. This figure lies with fair constancy within the limits of 45 and 65 per cent.

4. The ingestion of carbohydrate in sufficient quantities causes a definite and constant rise in the sugar content of the cerebrospinal fluid and disturbs the usual relationship between the sugar content of the cerebrospinal fluid and that of the blood.

5. Meningitis, whether tuberculous, staphylococcus or meningococcus, frequently gives a low sugar content of the cerebrospinal fluid, both as to actual milligrams per hundred cubic centimeters and in relation to that of the blood.

The literature shows a high sugar content of the cerebrospinal fluid in relation to the sugar content of the blood in cases of encephalitis.

Untreated cases of early cerebrospinal syphilis give a low actual and relative sugar content of the cerebrospinal fluid. Under treatment, this figure returns to normal.

²⁰ Achard, C., and Rouillard, J. Bull et mem soc med d hôp de Paris 45 130 (Feb 11) 1921

When considering the fact that the sugar content of the spinal fluid is lowered with a fair degree of constancy in cases of tuberculous, meningococcus and staphylococcus meningitis, one must remember that a low figure after intraspinal administration of antimeningococcus serum is of no diagnostic value.

VITAL CAPACITY AS A FUNCTIONAL TEST IN HEART DISEASE[†]

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To devise a simple test for estimating the functional capacity of the heart has been the aim of many investigators for several years. Many tests were advanced, most of them based primarily on the response of the heart to exercise. The majority of these tests have proved of very little value and are not being used today. Within the past decade, the study of the vital capacity of the lungs as a functional test in heart disease has gained favor with many clinicians, and favorable reports on the use of this test have been made by Peabody and Wentworth,¹ Ulrich and Nathanson² and others. Peabody and Wentworth¹ state that there is a definite relation between the vital capacity and the tendency to dyspnea, and have classified cardiac patients into four classes according to the heart's efficiency.

Patients with a vital capacity of 90 per cent or more of the normal standard were able to carry on their work with very little dyspnea. Patients with a vital capacity of from 70 to 90 per cent of normal became dyspneic on unusual exertion. Patients with a vital capacity of from 40 to 70 per cent of normal became dyspneic on moderate or slight exertion and those with a vital capacity of less than 40 per cent of the normal are decompensated patients and usually confined to bed.

Opitz,³ while admitting that a marked decrease in vital capacity signifies cardiac decompensation and that the percentage indicating its reduction may be employed as a measure of failure to compensate, questions greatly the assertion that the vital capacity portrays the condition of the patient more plastically than the blood pressure and pulse. He emphasizes also that the vital capacity does not change materially in those cardiac patients whose compensation is adequate.

* From the Department of Medicine, University of Minnesota Medical School and the Cardiac Section, United States Veterans' Bureau Clinic, District 10.

[†] Read before the combined staffs of Lymanhurst Hospital and Parkview Sanitarium, June 24, 1924.

1 Peabody, F W, and Wentworth, J A Clinical Studies of the Respiration IV The Vital Capacity and Its Relation to Dyspnea, Arch Int Med 20 443 (Sept) 1917

2 Ulrich, H L, and Nathanson, M H The Vital Capacity of the Lungs in Cardiac Disease, Minnesota Med 4 721 (Dec) 1921

3 Burton-Opitz, Russell Vital Capacity of "Cardiacs," J A M A 78 1686 (June 3) 1922

The present study was undertaken for the purpose of adding what little I may to a better understanding of the relationship between vital capacity and cardiac efficiency. The observations were made on a group of 207 cardiac patients at the U S Veterans' Bureau clinic. A thorough clinical study was made of each case, and only those cases were selected which had no complications outside the circulatory system that would in any way affect the vital capacity. The functional capacity of the heart was determined by a study of the history, symptoms,

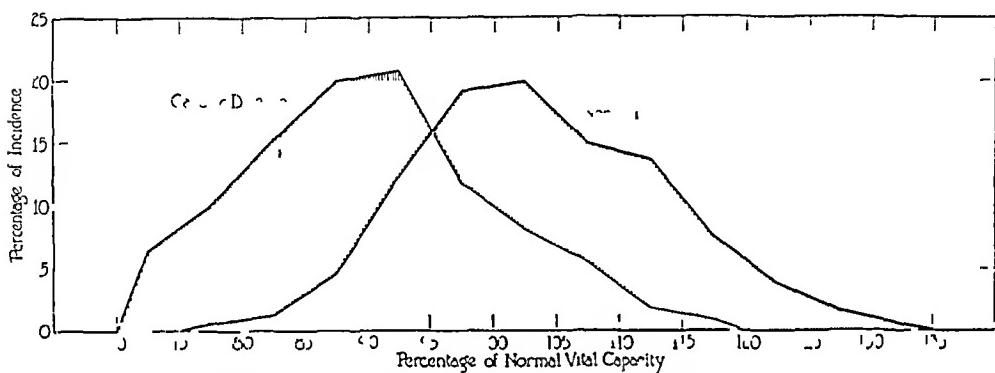


Chart 1—Vital capacity in Class 2a patients (111 cases) Organic, able to carry on, with slightly diminished physical activity

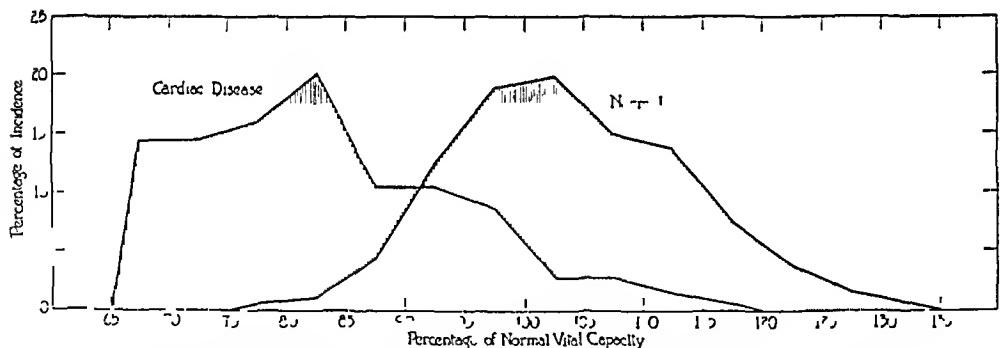


Chart 2—Vital capacity in Class 2b patients (69 cases) Organic, able to carry on, with greatly diminished physical activity

physical signs and the response to exercise, and the patients were then placed into one of five groups according to the classification of the Association of Cardiac Clinics

Class 1—Organic (able to carry on usual physical activity)

Class 2—Organic (able to carry on, *a*, slightly diminished physical activity, *b*, greatly diminished physical activity)

Class 3—Organic (unequal to any physical activity)

Class 4—Possible heart disease (doubtful murmurs, mainly functional, possibly organic)

Class 5—Potential (predisposing history of rheumatism, tonsillitis, etc.) The vital capacity was calculated by means of West's⁴ formula (body surface in square meters times, 2,500) The surface area was determined by the linear formula of DuBois and DuBois⁵ There were six cases in Class 1, that is, patients who never had any symptoms of heart disease and in whom the condition was discovered only during a routine examination The vital capacity in this group ranged from 100 per cent to 123 per cent of the normal The majority of the patients were either in Class 2a or Class 2b There was also a small group of twenty cases in Class 4 This group included the cardiac neuroses and other functional cardiac conditions The distribution of the vital capacities in each of these groups is shown in Table 1 and also by curves in comparison with the normal curve in Charts 1, 2 and 3

The normal curve used in these figures was prepared by Shepard and Myers⁶ from a study of over 3,500 male university students Their vital capacity determinations were made by all the various methods in use and the average used as the normal

TABLE 1—*Distribution of Vital Capacity in Cardiac Disease*

Percentage Normal Vital Capacity	Class 2a		Class 2b		Class 4	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Below 70			10	14.3	1	5.0
71-75	7	6.3	10	14.3		
76-80	11	10.0	11	15.7	2	10.0
81-85	17	15.3	14	20.0	0	0.0
86-90	22	20.0	7	10.0	1	5.0
91-95	23	20.7	7	10.0	5	25.0
96-100	13	11.7	6	8.6	6	30.0
101-105	9	8.1	2	2.9	2	10.0
106-110	6	5.4	2	2.9	1	5.0
111-115	2	1.8	1	1.4	1	5.0
116-120	1	0.9	0	0.0	1	5.0
Total	111	100.0	70	100.0	20	100.0

It will be seen that in Class 2a, patients who are able to carry on with slightly diminished physical activity, the average vital capacity of the group is between 86 and 90 per cent of normal, while in Class 2b, patients who are able to carry on with greatly diminished physical activity, the average is between 81 and 85 per cent of normal In Class 4, patients who have no organic condition, the average vital capacity is between 96 and 100 per cent of the normal A study of

⁴ West, H F Clinical Studies on Respiration A Comparison of Various Standards for Normal Vital Capacity of the Lungs, Arch Int Med **25** 306 (March) 1920

⁵ DuBois, D, and DuBois, E F A Formula to Estimate Approximate Surface Area if Height and Weight be Known, Arch Int Med **17** 863 (June) 1916

⁶ Shepard, W P, and Myers, J A Personal communication (to be published)

the curves in these various groups shows that the distribution follows very close to the normal curve, although there is a lowering and shifting to the left of the curves in Class 2a and Class 2b and slightly in Class 4. There is very little difference, however, between the curves of Class 2a and Class 2b. These results tend to show that while the vital capacity is usually reduced in the majority of ambulant cardiac patients, the range of distribution is very variable and cannot be limited by any class or group. The difference between the group which was

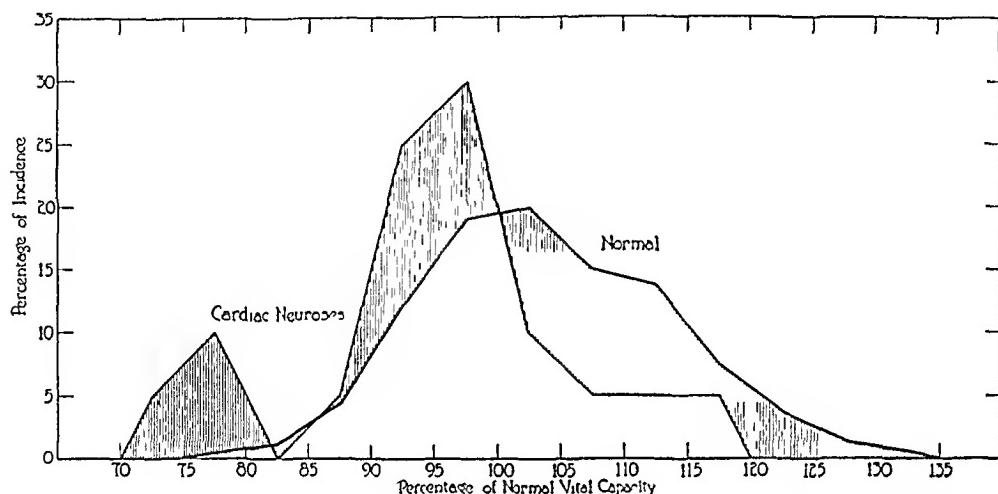


Chart 3—Vital capacity in Class 4 patients, cardiac neuroses (20 cases)

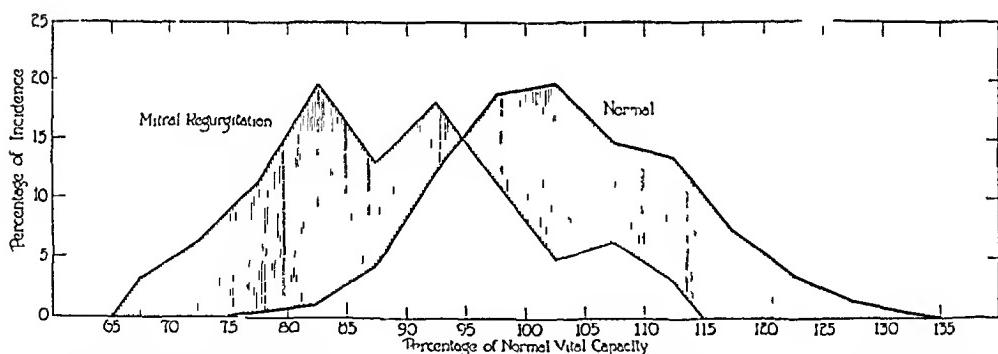


Chart 4—Vital capacity in chronic valvular disease with mitral regurgitation (60 cases)

able to carry on with slightly diminished activity and the group which was able to carry on only with greatly diminished activity is not marked, although the latter group does show a greater number with lower vital capacities.

A study of this series of cases was made also with a view to determine whether there is any relation between the type of lesion and the vital capacity. The results are shown in Table 2 and Charts 4 to 8, inclusive.

The average vital capacity is lowest in the group in which more than one valve is affected, being from 76 to 80 per cent of normal. In mitral stenosis the average was between 81 and 85 per cent of normal, while in mitral regurgitation, aortic regurgitation and the myocardial insufficiencies the average vital capacity was the same, being between 86 and 90 per cent of normal. In the patients affected with aortic regurgitation there was a tendency for the distribution to be within a prescribed limit, the majority falling within 86 and 100 per cent of normal. In the other groups, the tendency was to follow the normal curve, although in each of them the abnormal curve is lowered and shifted to the left. These results agree with the findings of Peabody and Wentworth,¹ that the vital capacity tends to be lower in mitral disease than in aortic disease and also that the vital capacity depends more on the severity of the lesion than on the type of lesion.

TABLE 2.—*Distribution of Vital Capacity in Various Types of Heart Disease*

Percent age	Mitral Regurgitation		Mitral Stenosis		Aortic Regurgitation		Aortic and Mitral Disease		Myocardial Conditions	
	Normal Vital Capacity	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases
Below 70	2	33	2	63			3	15.0	2	4.2
71-75	4	66	2	63	1	5.0	4	20.0	5	10.6
76-80	7	11.6	4	12.5	1	5.0	5	25.0	5	10.6
81-85	12	20.0	8	25.0	0	0.0	2	10.0	8	17.0
86-90	8	13.3	5	15.6	8	40.0	0	0.0	8	17.0
91-95	11	18.3	3	9.4	2	10.0	3	15.0	11	23.4
96-100	7	11.6	4	12.5	4	20.0	2	10.0	2	4.3
101-105	3	5.0	3	9.4	2	10.0	1	5.0	2	4.3
106-110	1	6.6	1	3.1	1	5.0	0	0.0	2	4.3
111-115	2	3.3	0	0.0	1	5.0	0	0.0	1	2.1
116-120	0	0.0	0	0.0	0	0.0	0	0.0	1	2.1
Total	60	100.0	32	100.0	20	100.0	20	100.0	47	100.0

COMMENT

That the vital capacity in heart disease bears a relationship to the symptom dyspnea, there is no doubt, but that the relationship is definite and the reduction in vital capacity parallels the reduction in cardiac efficiency is not shown by the results obtained in this group of cases. Several other factors must be taken into consideration in determining the cause of reduced vital capacity and its relation to cardiac efficiency. The vasomotor system is a great factor here, as it is in all tests for cardiac efficiency. Mechanical factors which interfere with the movements of the chest wall, such as rigidity of the bony framework, ankylosis of the costal joints, weakness of the intercostal muscles, and so forth, must be considered. Conditions within the chest itself, such as pleural effusion, emphysema and cardiac enlargement may influence the vital capacity, also conditions which cause increased abdominal pressure, such as enlarged liver, abdominal tumors and ascites.

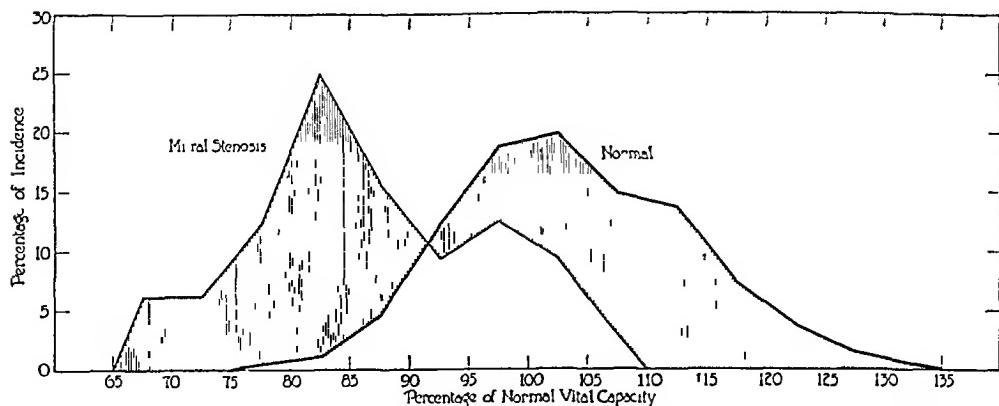


Chart 5—Vital capacity in chronic valvular disease with mitral stenosis (32 cases)

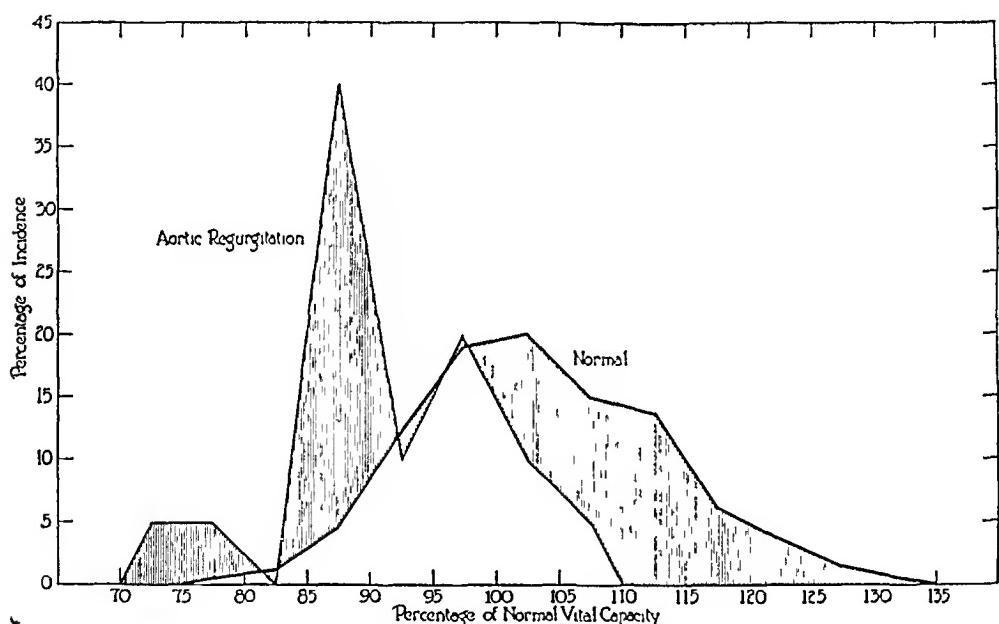


Chart 6—Vital capacity in chronic valvular disease with aortic regurgitation (20 cases)

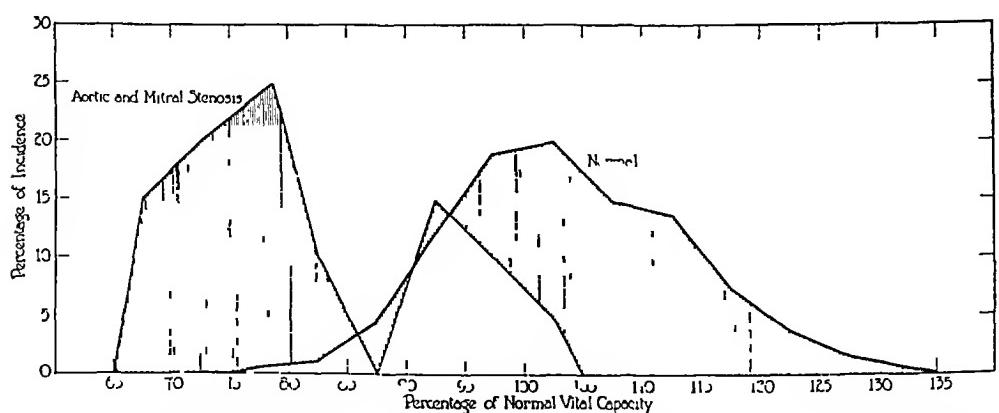


Chart 7—Vital capacity in chronic valvular disease with aortic regurgitation and mitral stenosis (20 cases)

The primary cause of dyspnea is best explained by Siebeck,⁷ who states that it is due to an engorgement of the capillaries of the lung alveoli, which in turn causes a distention of the alveolar walls with an increase of fibrous tissue and a resultant inelasticity of the alveolar walls. Pathologic examination of the lungs of passive congestion bears this out. Dyspnea, therefore, is due primarily to an alveolar insufficiency. This insufficiency may vary in different persons with the same amount of alveolar tension, and the same amount of alveolar insufficiency may produce varying degrees of symptomatology in different persons, just as an increase in arterial tension does not affect all hearts in the same way. This may in a measure explain the variability of the vital capacity readings in each clinical group. Also, as the range of the normal vital capacity varies from 75 to 135 per cent of the theoretic

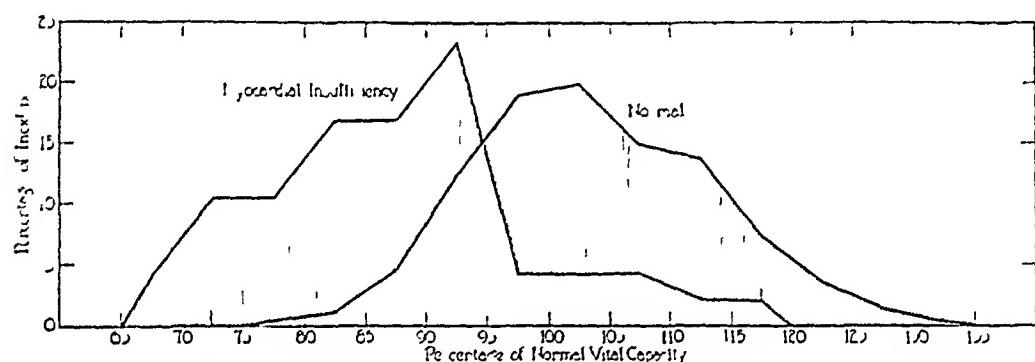


Chart 8—Vital capacity in cardiac disease with myocardial insufficiency (47 cases)

100 per cent, so the range of the vital capacity in this group of cases, although lowered, varies from 60 to 120 per cent of the theoretic 100 per cent. Therefore, a vital capacity reading in any given heart condition, unless it was very low, would not give us any conclusive information, as there is no way of determining its relation to the normal curve. A subject may have a vital capacity of 100 per cent and still be greatly reduced when compared to a normal person with 135 per cent

SUMMARY

- 1 Vital capacity is of value in the study of heart conditions
- 2 There is no definite relationship between the vital capacity and cardiac efficiency in ambulant cardiac patients
- 3 There is no definite relationship between the vital capacity and the type of heart lesion

⁷ Siebeck, R. Ueber die Beeinflussung der Atemmechanik durch Krankhaften Zustand des Respiration und Kreislaufapparates, Deutsch Arch f klin Med **100** 204, 1910.

NOTES ON THE THERAPEUTIC VALUE OF PNEUMOCOCCUS ANTIBODY SOLUTION SUBCUTANEOUSLY ADMINISTERED IN LOBAR PNEUMONIA¹

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AND
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The work reported in this article is concerned with our findings at Long Island College Hospital, during the fall, winter and spring of 1923-1924, as a part of a clinical experiment with the subcutaneous administration of pneumococcus antibody solution pursued under the supervision of the influenza commission in the cities of New York, Boston, Cincinnati and Chicago. It seemed desirable to study the effect of antibody solution administered subcutaneously, largely because previous workers seemed to be agreed that the reactions following intravenous inoculation of antibody solution are often severe and sometimes actually dangerous to the patient. In the interests of uniformity and in order to provide comparable results, the experimental clinical work was pursued in accordance with the following plan outlined by the influenza commission.

SELECTION OF CASES

1 Every case giving a typical history of chill, fever, pain in the side and cough with rusty sputum, together with typical physical signs of consolidation, as indicated by dulness, bronchial breathing and bronchophony is included. The area of consolidation need not be extensive.

2 Included also are cases without a typical history but with frank physical signs of consolidation, when there is a reasonable certainty that these signs are not caused by infarct, tuberculosis, tumor, or other organic disease not lobar pneumonia.

3 Cases with typical history and symptoms of lobar pneumonia, even if physical findings are negative, provided a definite shadow is demonstrated by roentgen-ray examination, are included.

4 Included also are cases in which the history and physical findings are suggestive but not typical of lobar pneumonia, provided the patient's sputum shows pneumococcus Types I, II and III.

¹ From the department of bacteriology, Hoagland Laboratory, and the department of medicine, Long Island College Hospital

PLAN OF PROCEDURE AS OUTLINED BY THE INFLUENZA COMMISSION

1 In every hospital cooperating in this study, there should be some one person responsible for, and having general supervision of, the experiment

2 Each ward will be considered an experimental unit Every case of lobar pneumonia admitted to a particular ward will be numbered consecutively First case, 1, second case, 2, and so on

3 Every case receiving an even number shall have the antibody treatment The odd numbered cases will not receive antibody treatment, but in other respects will be handled like the antibody cases In the case of our particular work at Long Island College Hospital, the foregoing plan was deviated from to the extent of administering antibody solution to one half of the Type I pneumococcus pneumonia patients in the series, and to certain of the remainder of the Type I pneumonia patients administering Type I pneumococcus antiserum By this means, it was hoped to obtain some data on the comparative value of antibody solution and antiserum in Type I infections Also, on two occasions, when the supply of antibody solution was temporarily exhausted, the sequence was broken to the extent that an even numbered case failed to receive antibody solution, and vice versa

4 In order to minimize the personal equation in the diagnosis and effect of treatment, it is necessary that both the antibody and control cases come under the direct observation of the same person, in each experimental unit or ward

TREATMENT

1 Antibody solution will be administered subcutaneously in the flank or anterior abdominal wall The first injection will be given as soon as the clinical diagnosis of lobar pneumonia has been made In certain of the cases in our series, subcutaneous administration of antibody solution subpectorally was resorted to

2 The initial dose of the antibody solution will be from 200 to 300 c c depending on the severity of the case The second dose (from 200 to 300 c c) will be administered from eight to twelve hours after the first dose The amount of subsequent dosage will depend on the severity of the infection and the result produced by the first two injections

3 In general, it may be said that in very severe cases from 200 to 300 c c should be given three times in the first twenty-four hours, during the second twenty-four hours, from 200 to 300 c c twice a day Smaller doses (from 100 to 150 c c) may be used after the first two

injections, if the patient has responded well, or if the infection is not severe Treatment should be continued until the temperature reaches from 99 to 100 F and remains there

NUMBER OF CASES STUDIED

The series on which this report is based consisted of forty-nine cases of pneumonia of which twenty-six were controls and twenty-three were treated with antibody solution Alternate patients were given antibody solution, as far as this was possible There were more controls than antibody cases because on two occasions our supply of antibody solution was exhausted and shipment was unavoidably delayed However, we

TABLE 1—Bacteriologic Classification of Cases by Sputum Typing

Micro organism	Number of Cases	Percentage Incidence
Pneumococcus Type I	15	30.61
Pneumococcus Type II	5	10.2
Pneumococcus Type III	2	4.08
Pneumococcus Type IV	24	48.97
Streptococcus	2	4.08
Undetermined	1	2.04

TABLE 2—Results of Blood Cultures

Micro-organism	Positive	Negative	Not Taken	Percentage of Positives
Pneumococcus Type I	6 (4 cases)	9 (8 cases)	5	40
Pneumococcus Type II	—	4	1	0
Pneumococcus Type III	—	2	—	0
Pneumococcus Type IV	5 (4 cases)	18 (16 cases)	4	21.79
Streptococcus hemolyticus	1 (sputum Type III pneumococcus)	1	1	50
Undetermined	—	1	—	0

would emphasize that in the series of cases which comprise the experiment, there was nothing even remotely resembling a selection of cases

We are perfectly frank in admitting that the series on which the report is based is small in number However, the fact that the work was quite rigorously controlled and that there was no selection of cases makes the results of comparative value

BACTERIOLOGIC CLASSIFICATION OF CASES

The methods employed in determining the specific type of pneumococcus responsible for the infection in each case were (1) a rapid method,¹ (2) the Mouse method, (3) the Avery method, and (4) blood cultures whenever possible The diagnostic serums used for typing were supplied by the New York state board of health

¹ Oliver, W. W. J. Infect. Dis. 27: 310 (Oct.) 1920, ibid 29: 518 (Nov.) 1921

Two rather unusual cases, from the bacteriologic standpoint, were encountered in the series. The first case was one of lobar pneumonia, in which the sputum contained a Type III pneumococcus, as demonstrated by the Mouse method, the Avery method, and a rapid method. On the same day that the sputum typing was performed, a blood culture was made which, on twenty-four hours incubation at 37.5°C., revealed a hemolytic streptococcus in pure culture. The second was a control case untreated with specific therapy. He was an East Indian, aged 25, who was admitted to the hospital on the fourth day of his illness and died on the seventeenth day. The clinical diagnosis was a "massive bronchopneumonia." On the fifth day of his illness, a sputum typing, done by the Mouse method and the Avery method, revealed a Type II irregular pneumococcus. A blood culture, taken on the same day, remained sterile on ten days incubation at 37.5°C. The seventeenth day of the disease, another blood culture was taken which revealed over 1,000 colonies per cubic centimeter of a Type I pneumococcus in pure culture. A postmortem lung culture was also positive for Type I pneumococcus in pure culture.

NATURE OF ANTIBODY SOLUTION

The pneumococcus antibody solution employed in the following experiments was prepared by F. M. Huntoon,² and was supplied by the Mulford Laboratories. Huntoon's method of dissociation of antibody from its antigen represents an extension and refinement of a method previously described by Gay and Chickering.³ To a mixture of Type I, Type II and Type III pneumococcus antiserum is added an equal volume of a heavy suspension of living pneumococci, Types I, II and III. This mixture is allowed to stand for one hour at 37.5°C., or for twelve hours at 20°C., this amount of time allows for a union of specific antibodies to specific antigens. The pneumococci are then thrown down with a centrifuge, and the micro-organisms are washed with physiologic sodium chloride solution, at almost the freezing point, in order to remove traces of horse serum. The washed sediment is next suspended in salt solution containing 0.25 per cent sodium bicarbonate and heated from thirty minutes to one hour at 55°C. By such treatment, the antibodies are dissociated from the antigen-antibody complex. The mixture is then centrifugated, and the removed supernatant fluid, which contains the antibodies, is chilled, recentrifugated and finally filtered through a filter candle. The final solution is almost completely protein free, and may contain as low as 0.035 mg. of nitrogen per cubic centimeter.

² Huntoon, F. M. J. Immunol. 6: 117 (March) 1921

³ Gay and Chickering. J. Exper. Med. 21: 389, 1915

METHOD OF ADMINISTRATION OF ANTIBODY SOLUTION

As the previous intravenous use of pneumococcus antibody solution had been attended by severe reactions which were occasionally harmful and, in a few instances, fatal, it became of more than academic interest to find a new method for its administration, if antibody solution was to become a therapeutic agent of general, practical clinical value. For this purpose, the subcutaneous route was chosen.

The first site selected was the abdominal skin, but it was soon discovered that it took almost an hour to introduce from 150 to 200 c.c. by the gravity method, even if the direction of the needle was changed repeatedly. It was then decided to try the skin of the lower axillary region, and this gave somewhat better results, because, as a rule, the skin in this area was more lax and the subcutaneous tissues permitted of greater distention by the fluid. In a further attempt to facilitate the administration, subpectoral injections were employed. This last method seemed to be the most satisfactory because the operation took less time, thereby causing less discomfort to the patient. Moreover, so far as could be determined, the absorption rate was not materially affected, because there was no increase in the incidence of reactions of any sort.

The actual technic of the injection was as follows. The skin area chosen was carefully cleaned with 3.5 per cent tincture of iodin. With a small hypodermic needle, from 1 to 2 per cent procain solution was injected intradermally until a raised area about the size of a 10 cent piece was produced. When successfully introduced, the procain gave rise to a very white area in which the hair follicles stood out prominently, so that the anesthetized area gave the appearance of a porous plaster. A needle, connected by tubing with a graduated cylinder which contained the antibody solution, was then introduced through the anesthetized area into the subcutaneous tissues, and the solution was allowed to flow in by the gravity method. On the average, twenty minutes sufficed for the subpectoral injection of 200 c.c. of antibody solution.

The following lot numbers of antibody solution were employed during the course of our experiment: 61269, 61487, 60785, 62179, 62477, 22179, 63339, 63310, 63737, 63898 and 64838.

The largest amount of antibody solution employed in any one case in our series was 3,400 c.c., of which the initial 1,900 c.c. was polyvalent and the remainder univalent Type I solution, and this was given in thirteen doses eight hours apart, in a case of Type I pneumococcus infection, with no apparent effect on the clinical course. In another case, of Type IV infection, 2,350 c.c. of polyvalent antibody solution was given in nine doses eight hours apart. The disease lasted seven days and terminated by lysis. Extension to another lobe occurred on the fifth

day. In view of the fact that these massive doses apparently did not materially influence the course of the disease, it was arbitrarily decided to discontinue antibody treatment in any given case after 1,000 cc had been given. The smallest amount of antibody solution used was 350 cc, and this case (Case 2) gave the most spectacular result in our series (Chart 6).

REACTIONS FOLLOWING SUBCUTANEOUS ADMINISTRATION OF ANTIBODY SOLUTION

From the beginning, it was felt that the antibody solution contained an irritant of some sort, because the patients invariably complained when the site of an injection was touched. This tenderness persisted for two or three days and was often very acute.

The incidence of chills or temperature reactions is apparently greatly reduced when the antibody solution is given subcutaneously, rather than intravenously. Cecil and Larsen,⁴ in commenting on the effect of intravenously administered antibody solution, say, "The reactions are often very uncomfortable and in certain cases are actually injurious to the patient." Conner,⁵ likewise, says of the intravenous administration of antibody solution, "The method has one serious drawback in that the immediate, or so-called thermal, reaction is sometimes very severe and may even result in death." Cecil and Larsen and Conner report that temperatures of 106 F., from twenty to forty-five minutes after the initial injection, are not uncommon.

In our series of twenty-three patients to whom antibody solution was administered subcutaneously, only two patients exhibited a chill and temperature rise following injection. In Case 2, a Type II pneumococcus infection, 200 cc of antibody solution were given as an initial injection at 3 p.m. Nine hours later, 150 cc of antibody solution was injected. One-half hour later, the patient had a severe chill which lasted for twelve minutes. Fifteen minutes after the chill had stopped, the temperature was 106.2 F. (rectal) as compared with 101.6 (rectal) before the second injection was given. In Case 12, a Type I pneumococcus infection, one-half hour after the thirteenth dose, which made a total of 3,400 cc of antibody solution which had been administered, there was a chill lasting thirty-eight minutes, and the temperature rose from 101 (rectal) to 105.8, followed by a sharp fall in the temperature to normal.

⁴ Cecil, R. L., and Larsen, N. P. Clinical and Bacteriologic Study of 1,000 Cases of Lobar Pneumonia, *J. A. M. A.* **79** 343 (July 29) 1922.

⁵ Conner, L. A. *Am. J. M. Sc.* **164** 832 (Dec.) 1922.

EFFECT OF ANTIBODY SOLUTION ON STERILIZING THE
BLOOD STREAM

In one out of the four cases of Type I infection in which blood cultures were positive, a striking example of the failure of antibody solution, when given subcutaneously, to sterilize the blood stream was brought out. This was Case 4, a Type I pneumonia patient, admitted on the third day of the disease. From the fifth to the eighth day of the disease, inclusive, he received 1,350 c.c. of antibody solution. The fifth day of the disease, a blood culture revealed 100 colonies of Type I pneumococcus per cubic centimeter. The seventh day, the colony count was 50 per cubic centimeter of blood. The twelfth day, three days before death, there were over 500 colonies of Type I pneumococcus per cubic centimeter of circulating blood. A second patient, Case 37, with Type IV pneumococcus infection, was admitted on the third day of the disease. Antibody solution treatment was begun on admission and

TABLE 3—*Complications in Antibody Treated and Control Cases*

Type of Complication	Antibody Series	Control Series
Extension	5	4
Pleural effusion	0	1
Otitis media	2	1
Cellulitis	1	0
Lung abscess	0	1
Phlebitis	0	1
Abscess of arm	1	0
Ischiorectal abscess	1	0
Urteritis	1 (on 11th day)	1 (Type 1 serum case)
Total	11	9

carried on through the fifth day of the disease, the total amount of antibody solution which he received being 1,000 c.c. The fourth day of his illness, a blood culture was sterile. The eighth day of the disease, a blood culture revealed one colony per cubic centimeter of blood of a Type IV pneumococcus. This lack of result in the case of Type IV infection was rather to be expected from the fact that antibody solution contains only protective antibodies against the fixed pneumococcus types, combined with the experimentally demonstrated fact that only against a limited number of Type IV pneumococcus strains does antibody solution exhibit any protective action.

COMPLICATIONS

Table 3 gives a list of the complications which developed in the antibody treated cases and the control cases.

In this connection, we desire to describe in detail the complication that arose in Case 4. The patient had received three injections of antibody solution into the left axilla, three injections into the right axilla, and

two injections under the abdominal skin. Two days after the last injection, the entire right side of the patient, from the apex of the axilla to a point about one hand's breadth above the right iliac crest, was reddened, indurated, tender and hot, and could be made to pit on pressure. Hot wet compresses were applied, but no fluctuation occurred, possibly because he did not live long enough. The process had all the outward appearance of a cellulitis. No doubt, part of this reaction could be ascribed to the tenderness and pain following the subcutaneous injection of antibody solution that was noted in some degree in every case that received the antibody treatment.

TABLE 4.—Mortality in Antibody Treated and Control Cases

	Antibody		Controls		Total	
	Cases	Deaths, per Cent	Cases	Deaths, per Cent	Cases	Deaths, per Cent
Type I	7	28.57	8	25.0	15	26.66
Type II	4	0.0	1	0.0	5	0.0
Type III	2	50.0	0	0	2	50.0
Type IV	10	10.0	14	21.42	21	16.66
Streptococcus			1		1	
Hemolytic streptococcus			1		1	
Undetermined			1	100.0	1	100.0
Total	23	17.39	26	23.7	49	20.408
Average day of disease on which admitted		4.43		4.307		
Average age		32.860		31.23		

TABLE 5.—Effect of Antibody Solution as Compared with Type I Pneumococcus Antiserum in Type I Pneumonia

	Anti body	Per Cent	Serum	Per Cent	No Specific Treatment	Per Cent	Total, per Cent
Number of cases	7		6		2		15
Death rate	2	28.5	0	0	2	100	26.66
Extension	2	28.5	1	16.66	1	50	20
Urticaria			1	16.66			
Cellulitis (from infections)	1	14.28					
Ischiorectal abscess	1	14.28					
Otitis media	1	14.28					

EFFECT OF THE ANTIBODY SOLUTION ON THE COURSE OF THE DISEASE

In our limited series of antibody treated cases, there was no striking improvement noted from day to day even in the cases which seemed to be benefited. With the exception of Case 2, a Type II pneumococcus infection, in which a crisis was obtained after two injections of antibody solution, it was impossible to notice any marked signs of subjective clinical improvement. Notes on Case 31, a Type I pneumococcus infection, show that, after the first two doses of antibody solution, the pain in the chest was improved. While the treatment was going on, the patient was sufficiently comfortable to read the newspaper, although the temper-

ature rate and the respiration rate were not influenced and the disease apparently ran its self limited course, with a pseudocrisis on the seventh day and a real crisis on the eighth day. Even in the cases that were interpreted as improved, the pain caused by the injections usually over-

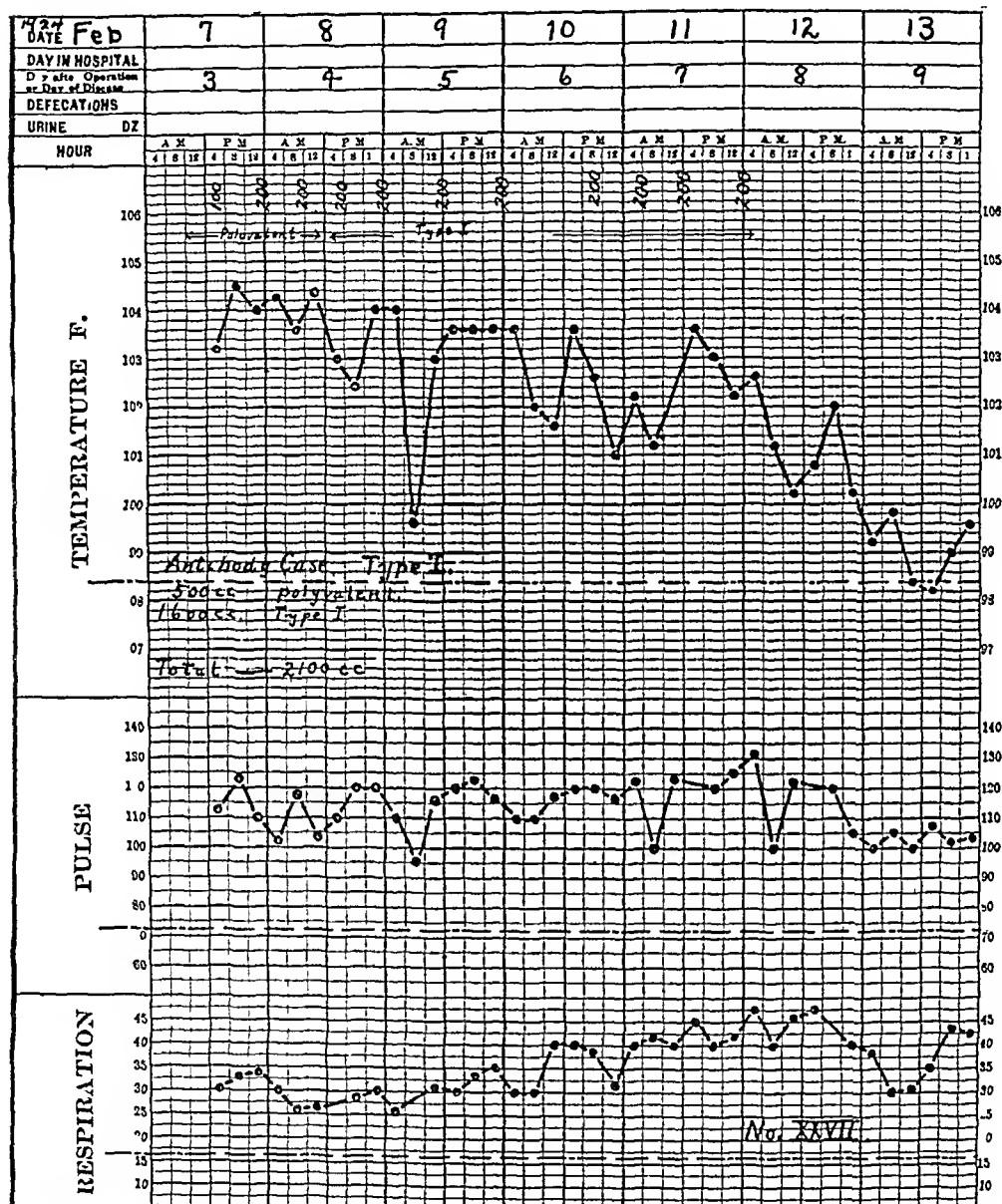


Fig 1.—Temperature, pulse and respiration in Case 27

shadowed any except the most striking clinical changes. In Case 6, the patient being a chronic alcoholic with delirium, although no sudden marked drop in temperature occurred, yet the general condition, on the eighth and ninth days, was unusually good in a type of case in which the prognosis is customarily considered poor. Finally, in Case 25, a

mild Type II pneumococcus infection, between the second and the fifth day of the patient's disease, he had received 800 c.c. of antibody solution. The crisis occurred on the fifth day of the disease, and resolution set in early. We feel that the antibody solution treatment favorably

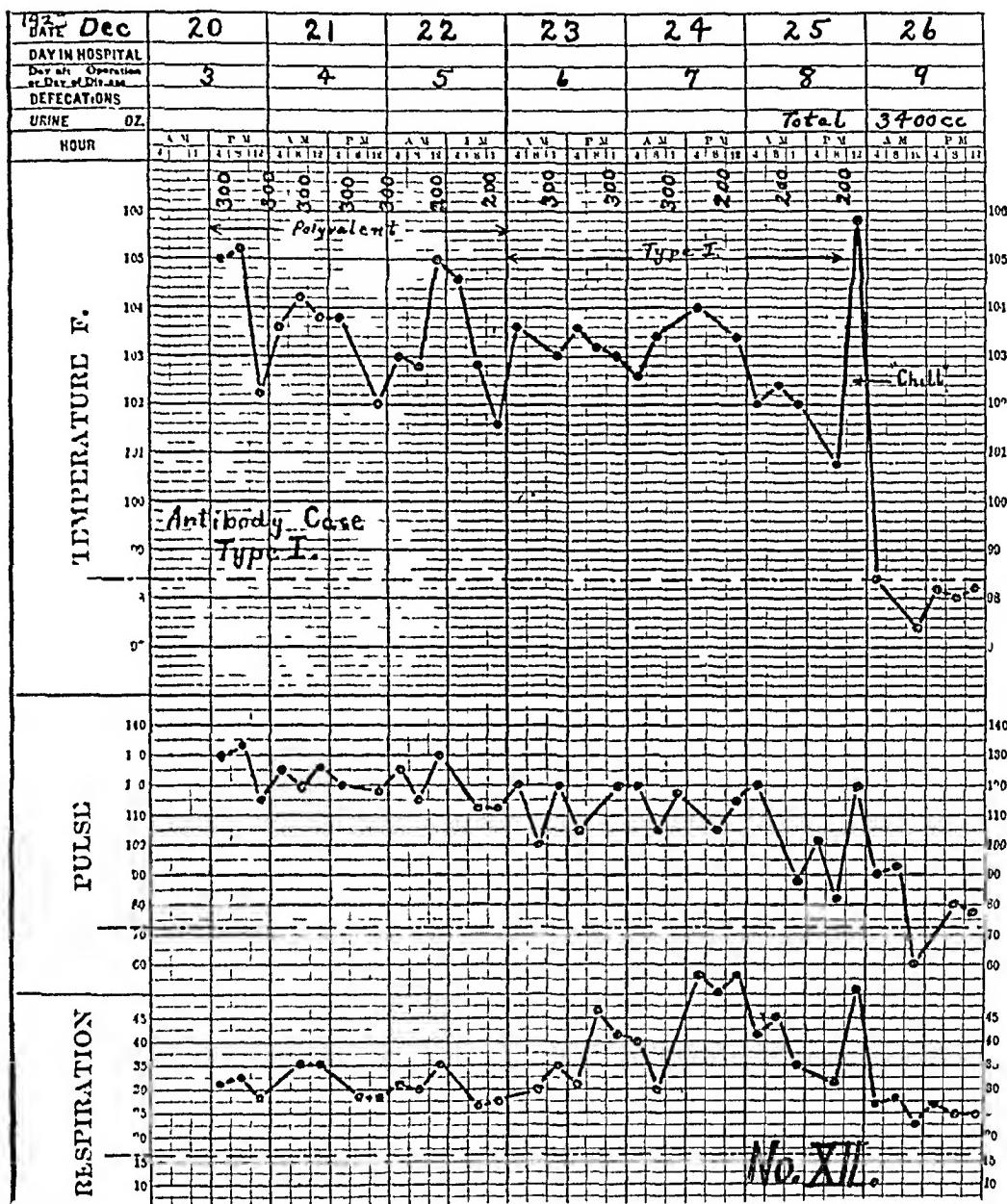


Fig 2.—Temperature, pulse and respiration in Case 12

influenced the course. The third day, the pain in the side was less marked, and he felt better in general.

In brief, then, in only four out of the twenty-three antibody solution treated cases was subjective improvement noted, and in three of the four cases mentioned above objective improvement also was observed.

SUMMARY OF ANTIBODY EFFECT

Subjective improvement was noted in four cases, objective improvement in three, subjective and objective improvement in three. No subjective or objective improvement was noted in nineteen cases, and

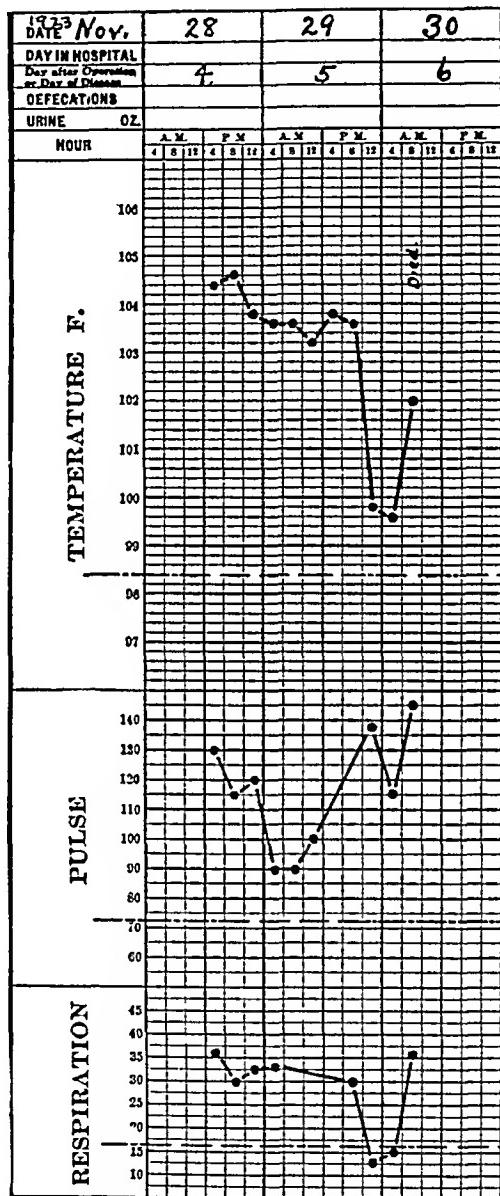


Fig. 3.—Temperature, pulse and respiration in Case 8, a control case of Type I infection

there was marked pain at the site of the injection in twenty-three cases

As a consideration of Table 4 will show, the striking feature is that the antibody treated cases of Type IV infection showed a little less than one-half the mortality (10 per cent) that was exhibited by the controls

(21.42 per cent) It also will be observed that the total mortality of the antibody treated cases plus the controls is 20.408 per cent, which is about the average mortality exhibited by pneumonia irrespective of the therapy employed.

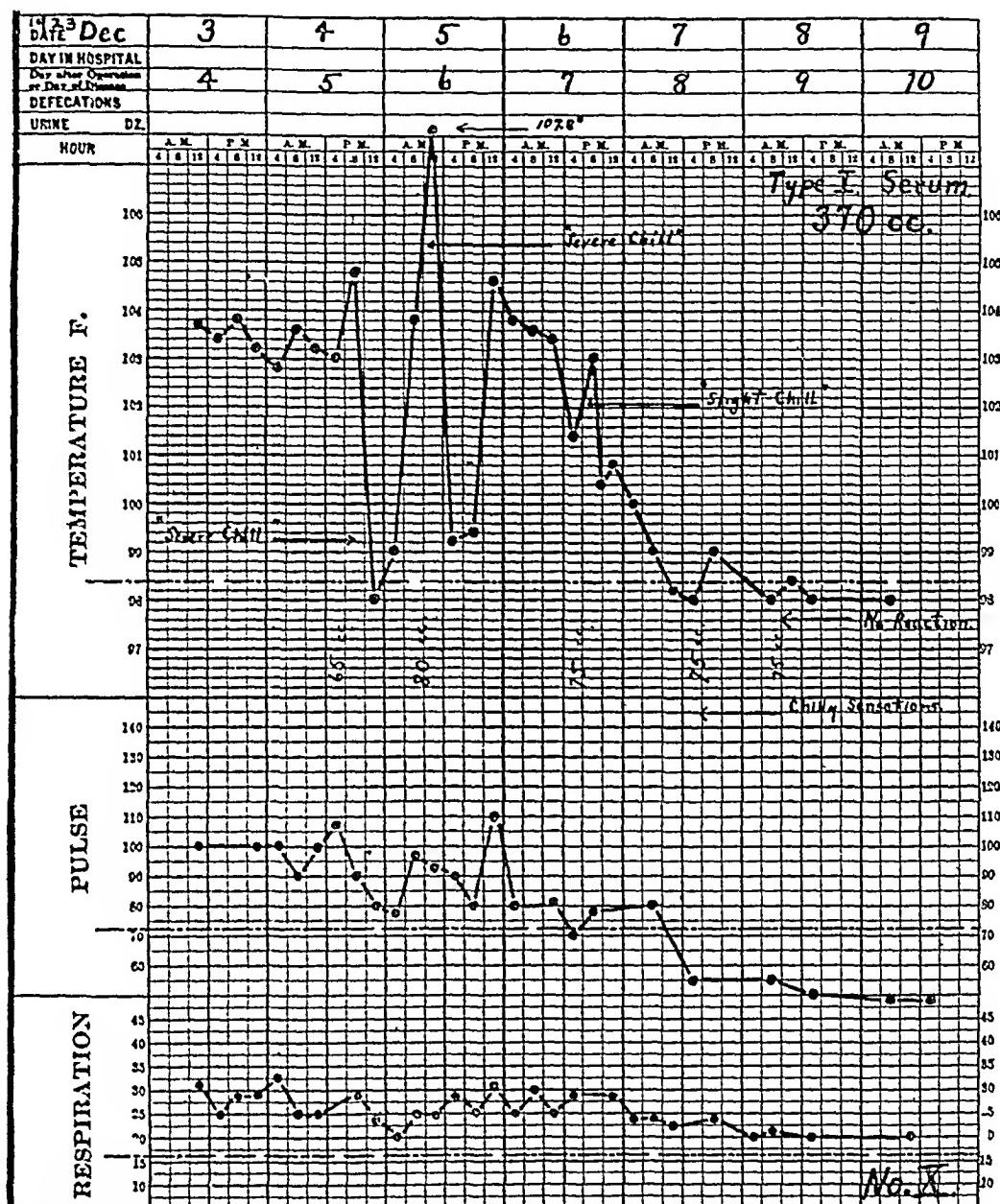


Fig 4.—Temperature, pulse and respiration in Case 10

CASE 27—A man, aged 21, a Norwegian, with a pneumococcus Type I pneumonia of the left lower lobe, at entrance before the type was known, had received 500 cc of polyvalent antibody solution, after which he received Type I antibody solution. The fifth day, there was a pseudocrisis, and that afternoon the temperature again reached its former peak. At this time, the left lower lobe showed signs of resolution. The morning of the sixth day, the picture had entirely changed. Cyanosis was intense and breathing labored.

By this time, the left upper lobe had become solid. The eighth day, antibody treatment was discontinued because he had become progressively worse. At this time, there was some pulmonary edema. Under heavy cardiac stimulation, the blood pressure was maintained and phlebotomy was not resorted to. The crisis occurred during the night of the eighth day.

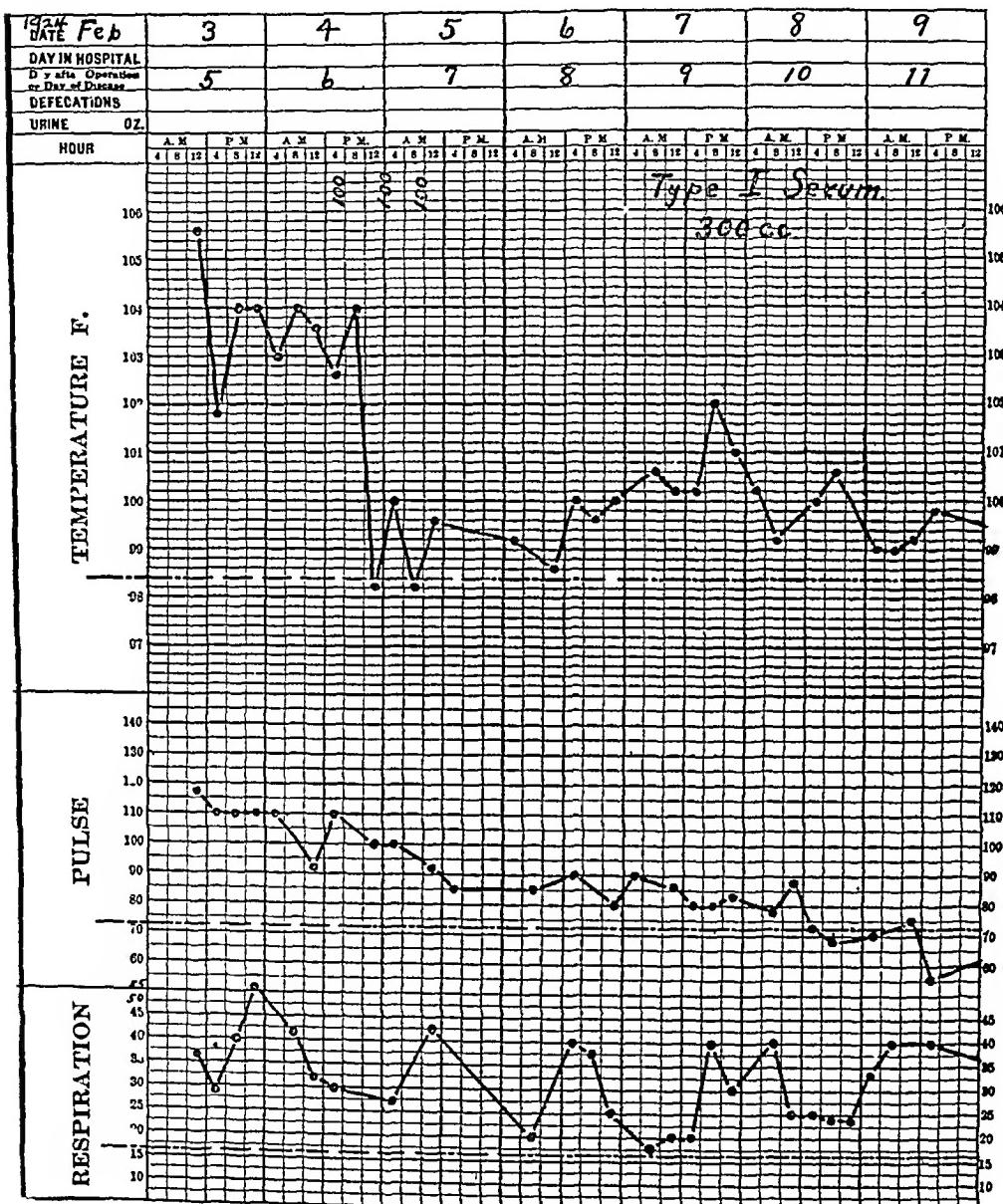


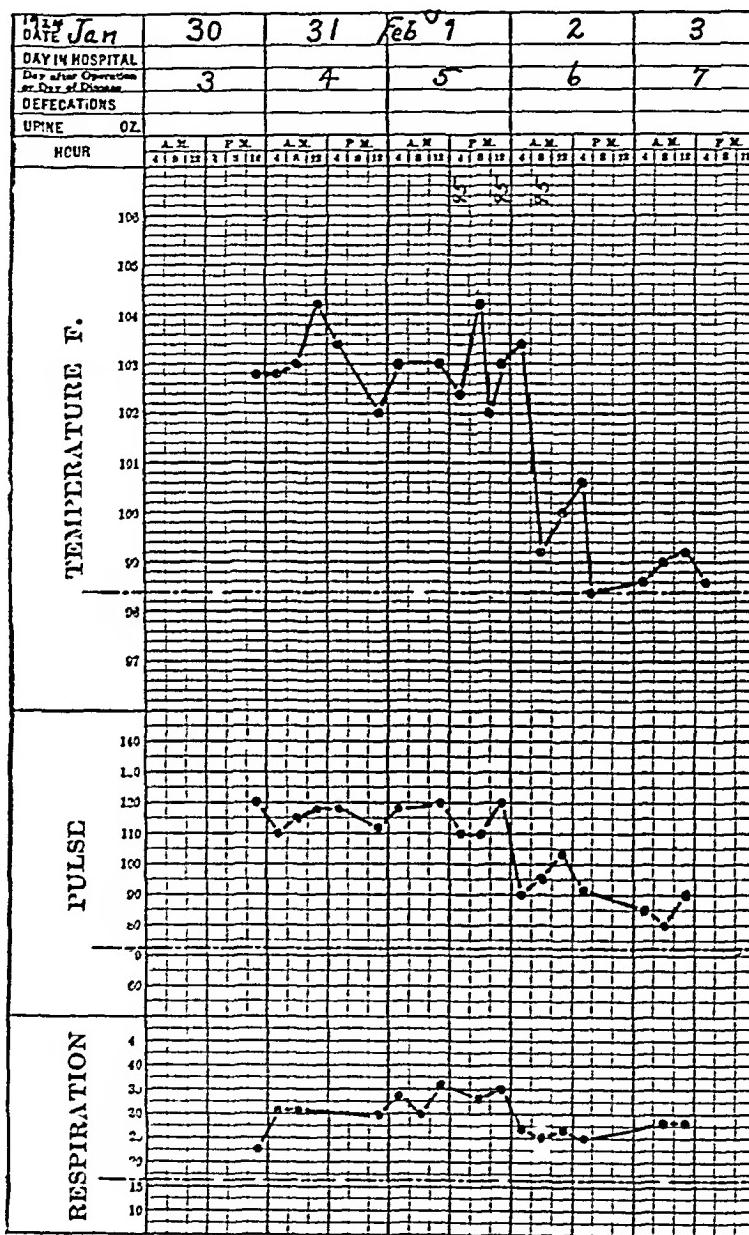
Fig 5.—Temperature, pulse and respiration in Case 24

In this case, in spite of vigorous antibody treatment, the symptoms were not alleviated, extension occurred, and the disease ran its course apparently uninfluenced in any way.

CASE 12.—A man, aged 26, a Brazilian, with pneumococcus Type I pneumonia of the left lower lobe, after 1,900 cc of polyvalent antibody solution had been given, was reported to be a Type I case, and, in the succeeding injections, Type I antibody solution was used. After the first three days of antibody

treatment, the only change that could be noticed was that he was a little more comfortable and had less pleuritic pain. About one half-hour after the thirteenth dose had been given, he had a chill which lasted thirty-eight minutes, and the temperature jumped from 101 F (rectal) to 105.8 followed by a sharp fall to 92.2, where it remained. This occurred on the ninth day of the disease.

In this case, the temperature was not brought to normal until the ninth day and then only after thirteen subcutaneous injections, totaling 3,400 cc.



There was also an irregularity in rate but not in force. From the beginning, the patient showed a peculiar drowsiness and during the second twenty-four hours he was mildly delirious. About thirty-six hours after entrance, the delirium became more marked, and it was necessary to give him a narcotic, after which respirations became very slow and shallow.

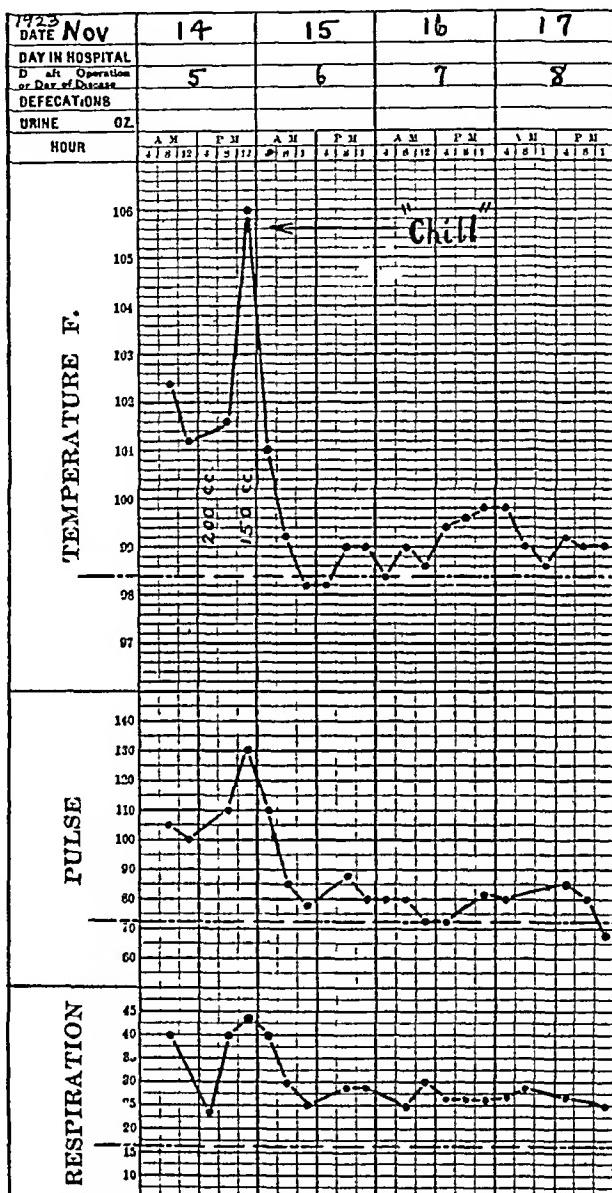


Fig 7.—Temperature, pulse and respiration in Case 2, a Type II pneumococcus pneumonia, 350 cc of antibody solution (polyvalent) was given.

This case illustrates a Type I infection complicated by mitral insufficiency in which the treatment consisted only of the ordinary supportive measures. There was no history of previous cardiac or rheumatic disease.

CASE 10.—A man, aged 23, a Filipino, with a Type I pneumococcus pneumonia of the left lower lobe, gave a poor response to Type I horse serum. Although treatment was begun on the fifth day, the temperature was not brought to normal until the eighth day. The first two injections were followed by such

severe chills that it was decided to procure a new lot of serum. Succeeding doses of a new lot produced only slight reactions, and the last injections produced no reactions of any kind. This patient had shown no sensitiveness to horse serum in the preliminary cutaneous tests.

CASE 24.—A man, an Italian, aged 25, with a pneumococcus Type I pneumonia of the right lower lobe, was given Type I horse serum treatment, beginning

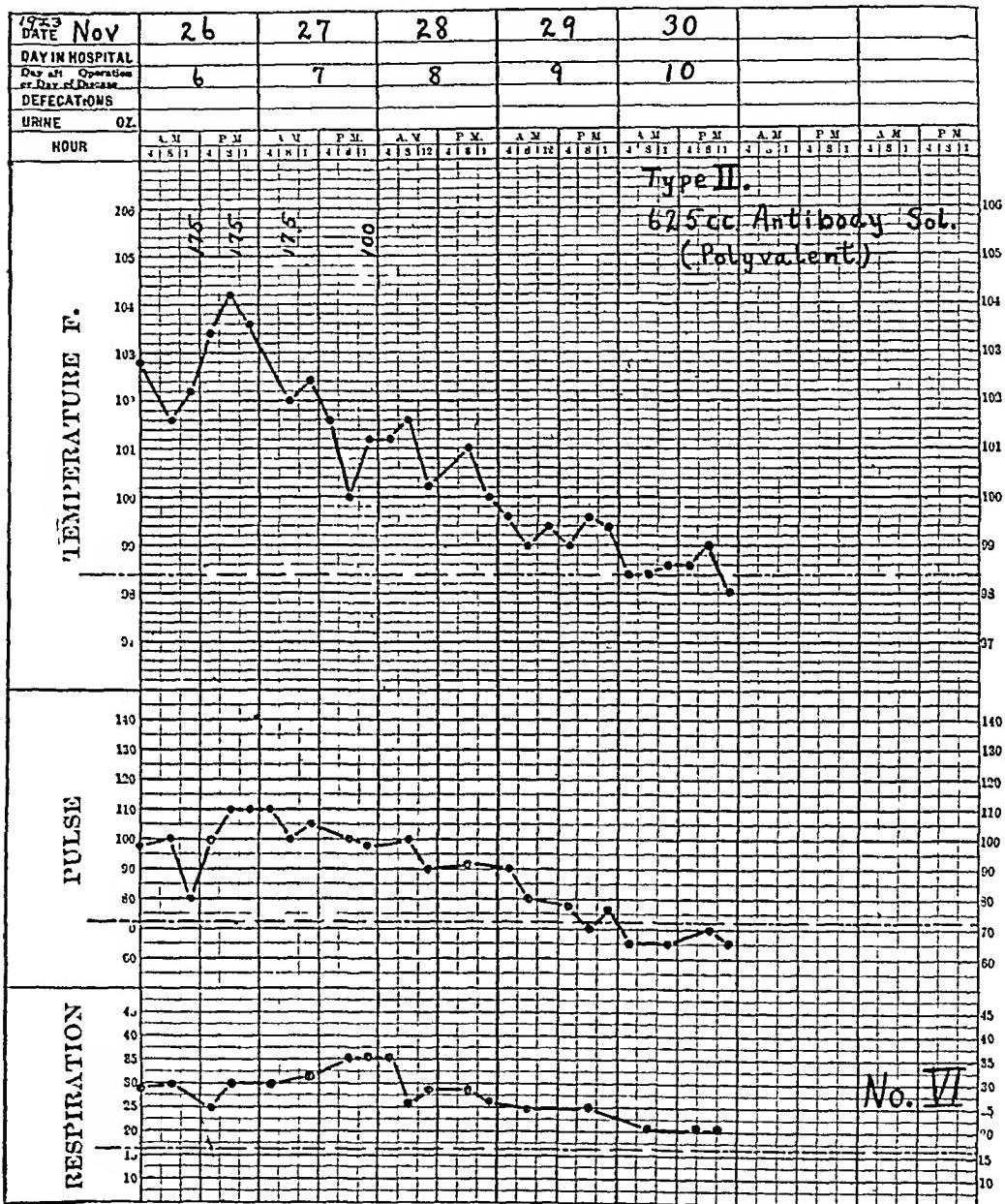


Fig 8.—Temperature, pulse and respiration in Case 6

on the evening of the sixth day. After the first dose of 100 cc, given intravenously, he had rather a severe chill. By midnight, the temperature had fallen to normal by crisis. Two more doses of 100 cc each were given at 1 a.m. and at 9 a.m. Marked delirium set in after the first dose.

In this case, we feel that the course was favorably influenced by Type I horse serum, in spite of the fact that the patient was in wild delirium for fully forty-eight hours after the temperature had come to normal.

CASE 20—A man, aged 21, an American, with pneumococcus Type I pneumonia of the right lower lobe, was admitted late on the third day of the disease, and serum treatment was not begun until the afternoon of the fifth day. After three doses of serum, eight hours apart, totaling 285 cc., crisis was obtained.

In this case, we feel that the course was favorably influenced by the serum treatment.

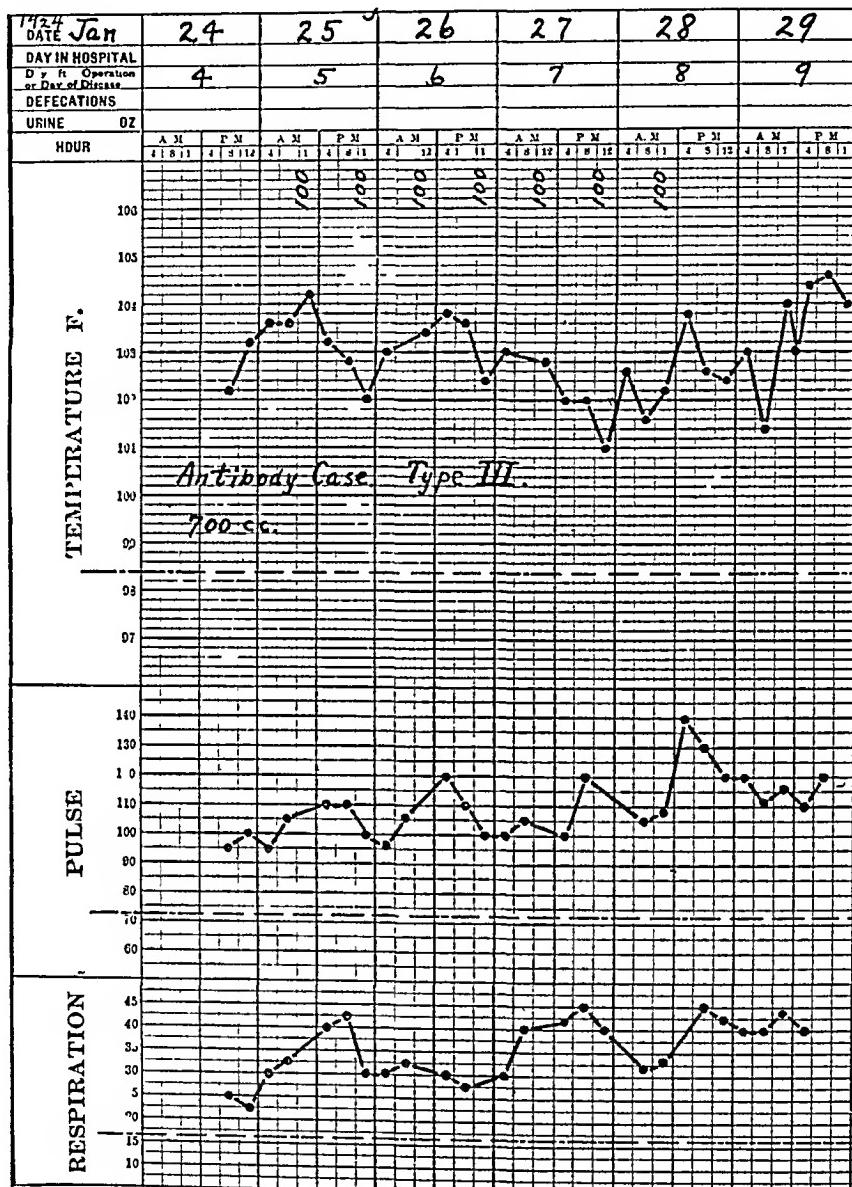


Fig 9.—Temperature, pulse and respiration in Case 17

CASE 2—A man, aged 45, an Italian, with Type II pneumococcus pneumonia of the right upper and middle lobes, had marked tenderness in the gallbladder region with an icteric tinge to the skin of the thorax and the abdomen. At 3 p m, 200 cc of antibody solution was given subcutaneously in the left axilla without reaction. At 12 p m, 150 cc was given subcutaneously. One-half hour later, there was a severe chill lasting twelve minutes, followed by a temperature of 106.2 F (rectal), then a sharp fall of temperature to 101,

at 4 a.m., and 99.2, at noon. The abdomen was softer and the right hypochondrium less sensitive.

This case shows a striking response to antibody treatment and illustrates the best clinical result obtained in the series.

CASE 6.—A man, aged 33, an American, who suffered from chronic alcoholism, had pneumococcus Type II pneumonia of the left lower lobe. The patient was given 625 cc of antibody solution. Although this case shows no sudden marked drop in temperature, the general condition, on the eighth and ninth days, was

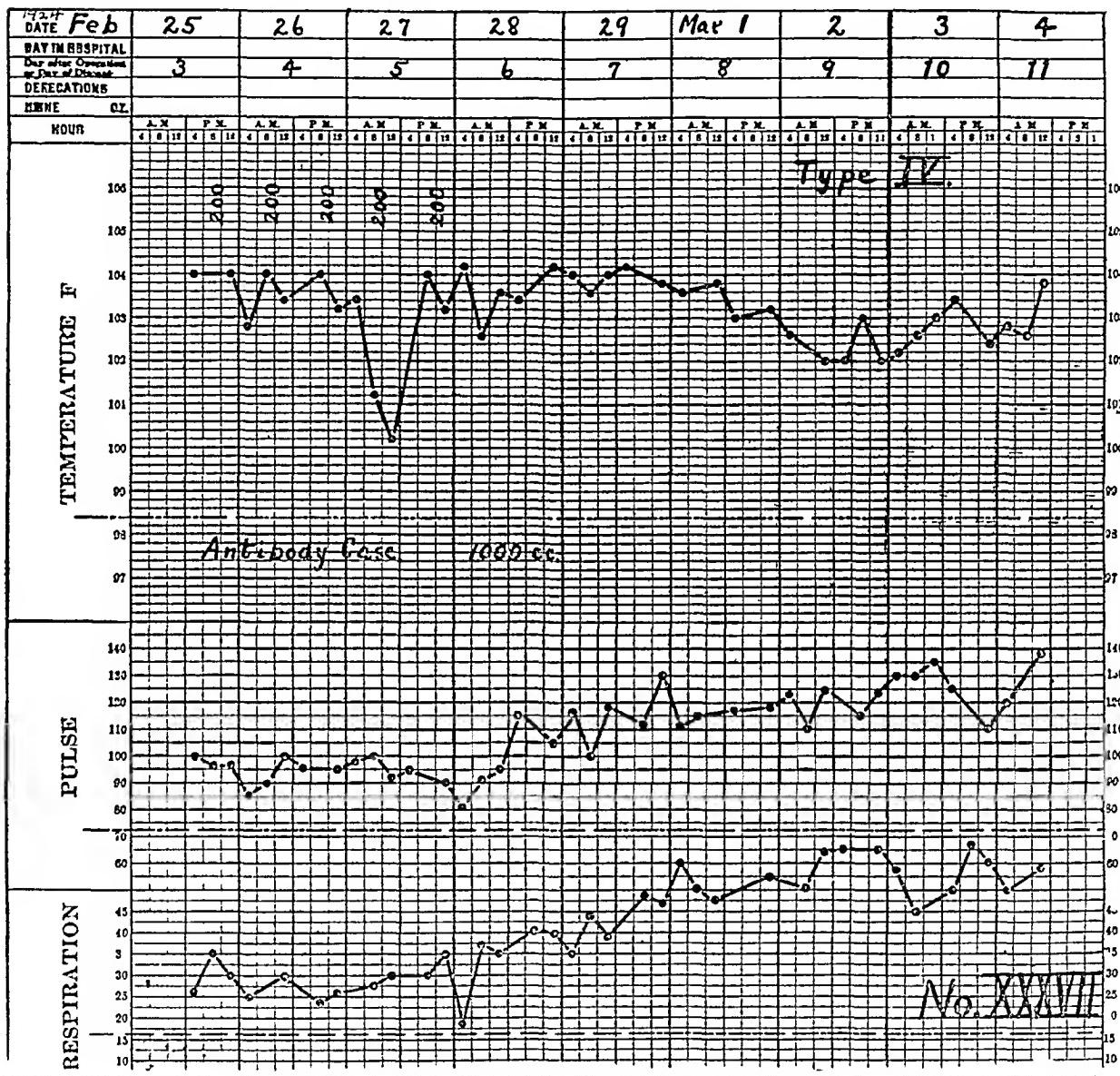


Fig 10.—Temperature, pulse and respiration in Case 37

unusually good, considering that the patient suffered from chronic alcoholism and that the pneumonia precipitated an attack of delirium tremens which was so marked that he had to be restrained.

CASE 17.—A man, aged 21, a Porto Rican, with a pneumococcus Type III pneumonia of the right lower lobe was admitted on the fourth day of the disease. The fifth day, blood culture showed a few colonies of hemolytic streptococcus. He received 100 cc polyvalent antibody solution every twelve hours for seven doses. By the seventh day, there were signs of extension to

the right middle and right upper lobes. Blood culture, the ninth day, was sterile. He died, the ninth day, of myocardial failure. There was no response to phlebotomy and all the cardiac stimulants.

In this case, there was no notable improvement under antibody treatment, and the process extended rapidly.

CASE 37.—A man, aged 26, a Swiss, was admitted with a Type IV pneumococcus pneumonia of the right lower lobe. After 800 cc of antibody solution,

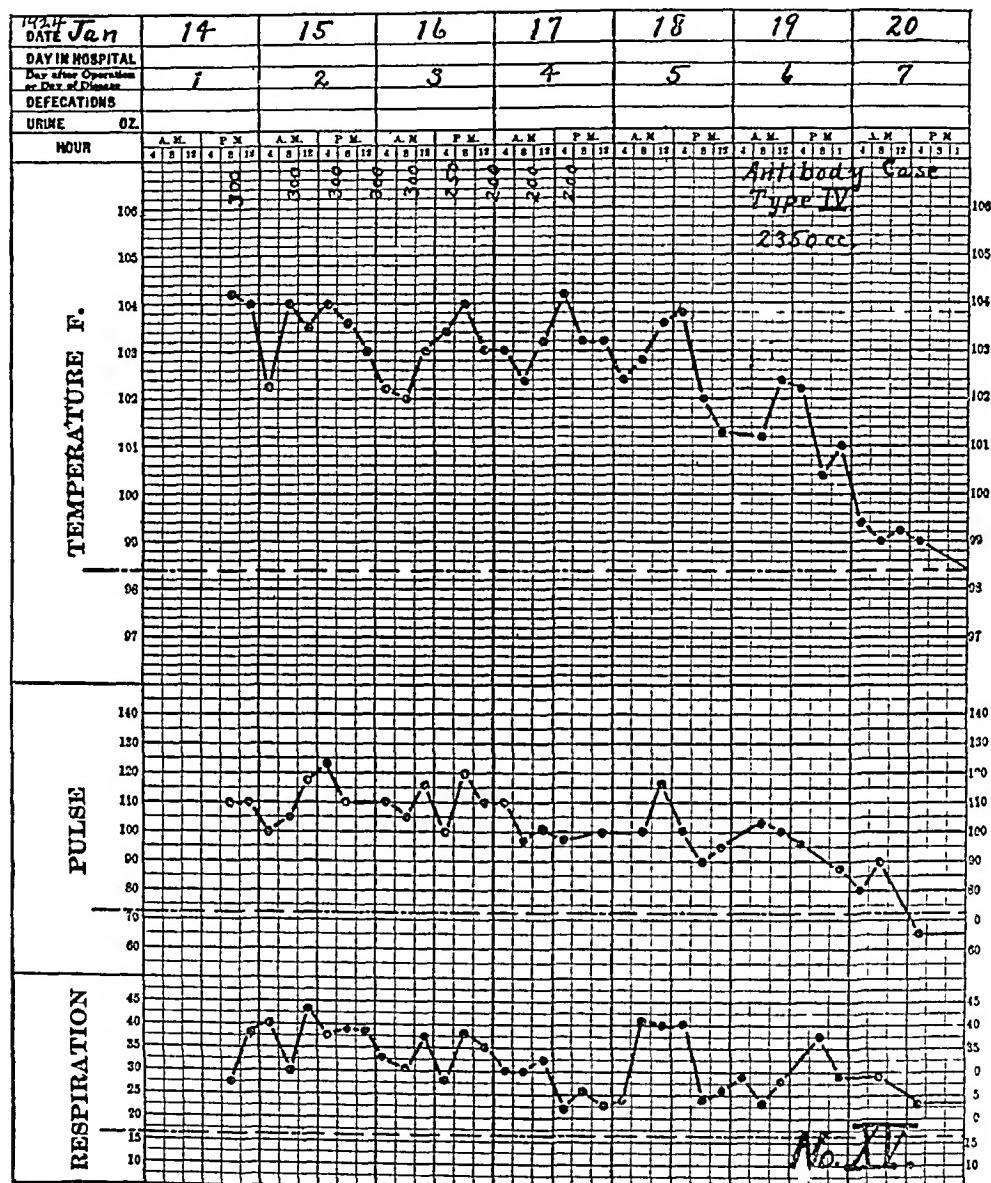


Fig. 11.—Temperature, pulse and respiration in Case 15

the temperature had fallen to 100.2 F., the pulse was 95, and respiration was 30. The night of the fifth day, the temperature had returned to 104. The sixth day, the right middle lobe was involved, and the seventh day, the left lower lobe as well. The eleventh day, the patient died of myocardial failure. Blood culture on the fourth day was sterile, and on the eighth day showed one colony per cubic centimeter of pneumococcus Type IV. Material obtained from the chest by postmortem puncture also showed a Type IV pneumococcus.

In this case, the progress was not influenced in any way, and the disease spread from one lobe to another in spite of vigorous antibody treatment.

CASE 15.—A man, aged 28, an American, with a pneumococcus Type IV pneumonia of the right middle and upper lobes, received nine doses of antibody solution, totaling 2,350 c.c., after which it was discontinued. This was a case which was obtained on the first day of the disease, the onset with chill occur-

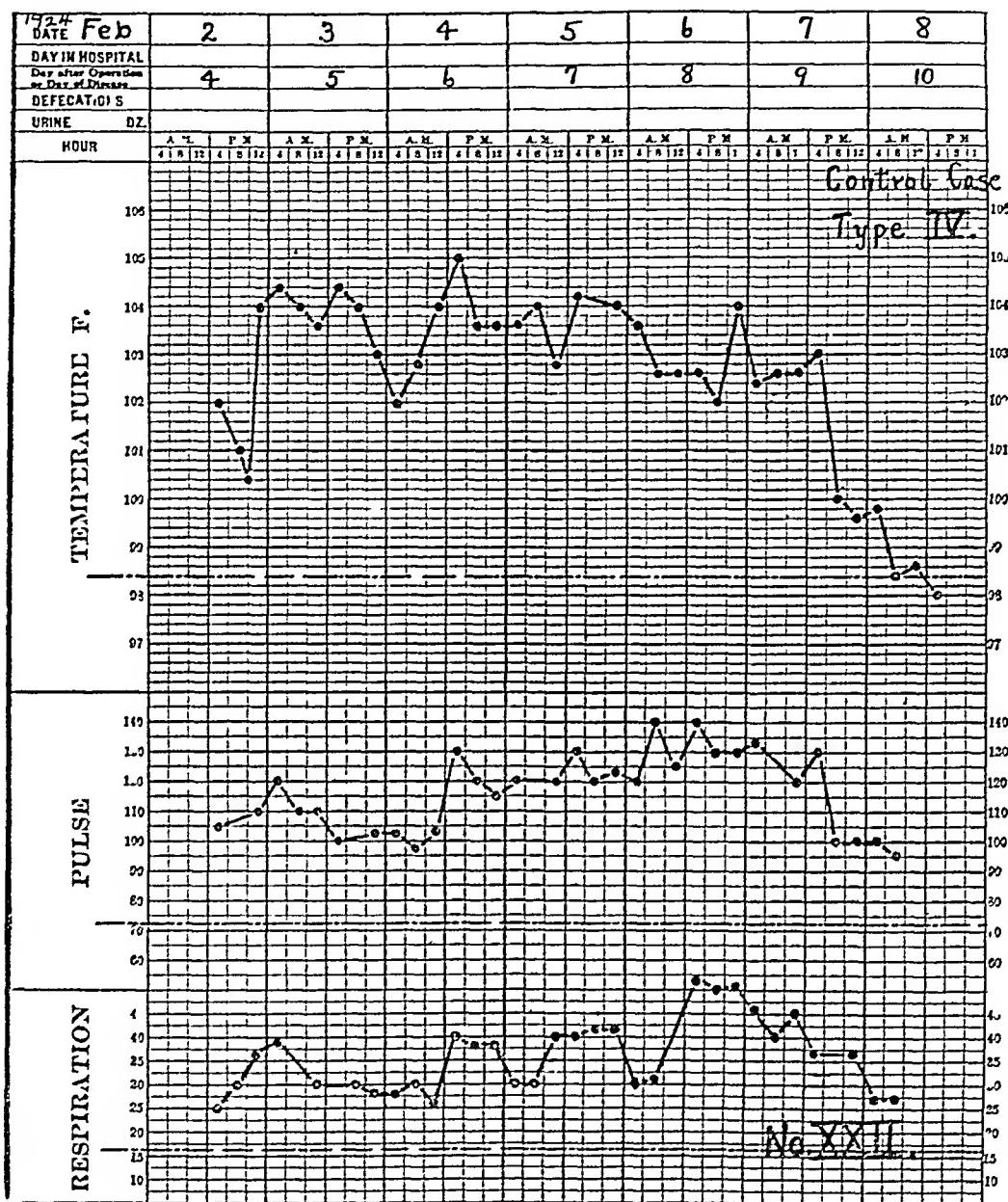


Fig. 12.—Temperature, pulse and respiration in Case 22

ring at noon, and the patient being admitted to the hospital at 7:55 p.m. In spite of vigorous antibody treatment, the process was not halted in the lobe originally involved, but, the fifth day, it extended to the right upper lobe and went on, ending by lysis on the seventh day.

CASE 22.—A man, aged 25, a Spaniard, with a right lower lobar pneumonia, was admitted, the fourth day of the disease, and the crisis occurred, the ninth day. There were no complications of any sort.

SUMMARY AND CONCLUSIONS

1 The subcutaneous administration of pneumococcus antibody solution is attended by a very low incidence of thermal reactions as compared with its intravenous use, as reported by Cecil and Larsen, and Conner.

2 The subcutaneous injection of pneumococcus antibody solution invariably produces a painful tissue reaction, and this may persist for days.

3 The subpectoral region seems to be the most favorable site for injecting pneumococcus antibody solution.

4 In our series of twenty-three cases treated by antibody solution, only four cases gave evidence of subjective and objective improvement, while the remaining nineteen cases, in our opinion, did not appear to be benefited by it.

5 Pneumococcus antibody solution administered subcutaneously did not, in our very limited experience, tend to sterilize the blood stream.

6 Subcutaneous antibody treatment is of less value in Type I pneumococcus infections than is Type I pneumococcus antiserum administered intravenously.

7 Subcutaneous antibody treatment does not appear to prevent extension of the pneumonic process from one lobe to another.

8 The best results were obtained in Type IV pneumococcus pneumonias in which the subcutaneous antibody treatment registered a mortality of 10 per cent as compared to a mortality of 21.42 per cent in the control Type IV cases. If these results were due to antibody solution, it would seem probable that they were attributable to a non-specific action of the solution.

Book Reviews

DIFFERENTIAL DIAGNOSIS VOL II By RICHARD C CABOT, M D, Professor of Medicine and of Social Ethics at Harvard University Third Edition Cloth Price, \$9.00 Pp 709, 254 illustrations Philadelphia W B Saunders Company, 1924

This edition represents an amplification of the cases in former editions. Three hundred and seventeen cases are analyzed and discussed in a quite novel manner, and are grouped according to symptomatology and physical findings. It is composed of nineteen chapters, a large portion of the work being devoted to abdominal tumors and enlargements and to such topics as vertigo, dyspepsia, diarrhea and edema. The book is printed in large type on good paper and is profusely illustrated. It is very readable, and contains a great amount of information gained from a large experience. It should be particularly valuable to the general practitioner in medicine.

CLINICAL AND EXPERIMENTAL STUDIES OF THE OBSTETRICAL PALSY OF PLEXUS BRACHIALIS By S G K BENTZON Copenhagen Levin and Munksgaard, 1922

After an extensive discussion of the literature on the symptomatology, etiology and pathology of birth palsies, Bentzon concludes that overstretching of the brachial plexus is the chief cause of the Duchenne-Erb's type, thereby endorsing the opinion of Clarke, Taylor and Trout. It is caused by lesions of the fifth and sixth cervical roots near the junction of these roots. The author made many anatomic and experimental studies in order to determine the reason for the peculiar distribution of the paralysis among the many muscles that are innervated by these nerves. The most constant finding is the fixation of the arm in inward rotation due to the fact that the subscapularis muscle is unaffected. It was found that the scaleni protected the proximal portions of these nerves against pressure, that traction on peripheral nerves is easily transmitted to the plexus, even to the roots, that by the use of a special apparatus by means of which the distance between the mastoid process and the homolateral acromioclavicular joint could be increased in still-born children, and by careful dissection, the entire plexus was easily exposed so that, in the various manipulations, degrees of stretching, place of rupture of nerves and probable manner of occurrence of these injuries were demonstrated. It is evident that when nerves are taut only slight amounts of pressure properly applied are necessary to cause great damage. The seven muscles most frequently affected in this type are innervated by the nerves which are shown to suffer the greatest stretching by this method.

The prognosis is considered as to the paralysis itself and as to the contractures with their sequelae. The prognosis is usually good because the lesion is due mainly to stretching and not to rupture of the nerves. Early treatment with physiotherapy influences the end-result greatly, particularly if begun before the development of contractures and deformities. The author discourages operations on the brachial plexus for relief of this condition.

Klumpke's type, i.e., lesions of the lower cervical and first dorsal nerves, is not discussed as fully as the Duchenne-Erb form. Pressure on or crushing of the nerves between the clavicle and the first rib apparently is the chief etiologic factor. Raising of the arms and shoulders, especially if the clavicle is elevated as well, causes great stretching of the lower nerves of the plexus.

notably the median and ulnar nerves. This type of palsy is more apt to occur in breech and face presentations. The prognosis is much less favorable in this type of palsy, and direct operations on the plexus are often indicated.

Very little is known of the pathology of either type because of the surprising paucity of necropsies.

The author presents thirty-one excellent case histories.

The various theories concerning palsies and the differential diagnosis of these conditions, as well as the physiology of the shoulder movement, are ably criticised and discussed.

Archives of Internal Medicine

VOLUME 35

MARCH, 1925

NUMBER 3

ALL DAY BLOOD SUGAR CURVES IN NONDIABETIC INDIVIDUALS AND IN DIABETIC PATIENTS WITH AND WITHOUT INSULIN*

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INTRODUCTION

Despite the many excellent studies on the use of insulin in diabetes, there has, as yet, been evolved no satisfactory routine method of regulating the dosage and the time of its administration. It is obviously to be desired that the doses be as small and the administrations as infrequent as possible. Moreover, with a diet adequate for maintenance and reasonable activity, the blood sugar concentration throughout the day must be held within normal limits. To accomplish this requires, first, an appreciation of what the normal blood sugar values throughout the day are and, second, an understanding of the effects that various diets and insulin dosages, and certain combinations of these, produce in diabetic patients. Only by intensive studies of the blood sugar concentration on large numbers of both normal persons and those in differing stages of the disease, can this knowledge be obtained. Our purpose, in this paper, is to present the results of such investigations, which we have made in this hospital during the last year, and to develop certain general rules for the use of insulin in the management of cases of diabetes. Incidentally, we will suggest a simple, practical method of estimating the full day blood sugar level in individual cases. First, blood sugar curves obtained from nondiabetic persons on adequate diets will be presented, then those from patients with diabetes of varying severity who were not being treated with insulin, and, finally, those from diabetic patients who were receiving insulin.

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MATERIAL AND METHODS

All the patients utilized were adults who had been under careful observation in the hospital for at least several days and were free of acidosis. The men were kept in a special metabolic ward while the women were in a general medical ward but closely watched. Certain nondiabetic patients served as controls. The food for all was prepared and weighed by a trained dietitian. For the sake of simplicity, as much as possible of the data relative to the individual patients is supplied in connection with the charts, and this is not repeated in the text.

The blood samples were removed from the veins at the elbow and analyzed by the method of Folin and Wu¹. The specimens collected during the day were oxalated and analyzed immediately, while, during the night, with the exception of a few, they were collected in tubes containing sodium fluorid and thymol, as recommended by Sander,² and the determinations made the next morning. In a few of the earlier night collections, a drop of formaldehyd was added to the blood, and the analysis immediately carried to the stage where the water-clear filtrate was obtained. This filtrate was then placed in an icebox until the next morning, when the analysis was completed. Controls on both methods of preserving the specimens showed no change in the sugar concentration after they had stood from twelve to eighteen hours.

DESCRIPTION OF DATA

Nondiabetic Patients—In Charts 1 to 6 are presented curves showing the hourly variations in blood sugar throughout twelve-hour periods on ward patients who were nondiabetic and had none of the other conditions commonly associated with hyperglycemia. As a group, it may be said of these that, with the food reasonably adequate and equally distributed among the three meals, the fluctuations in the concentration of blood sugar ranged from 0.075 to 0.155 per cent. It is also to be noted that the high points in the curves usually occurred one hour after the meals—the highest in three of the six, after breakfast, in two, after supper, in one, after lunch, and that there was a tendency for the curve to fall back to the fasting level within from one to two hours after each rise due to food.

Patients With Mild Diabetes Without Insulin—Charts 7, 8 and 9 present curves from patients with mild diabetes who were not receiving any insulin but who had, for some time, been managed on dietary

¹ Folin, O., and Wu, H. A System of Blood Analysis, Simplified and Improved Method for Determination of Sugar, *J. Biol. Chem.* **41** 367-374 (March) 1920.

² Sander, F. V. Preservation of Blood for Chemical Analysis, *J. Biol. Chem.* **58** 1-15 (Nov.) 1923.

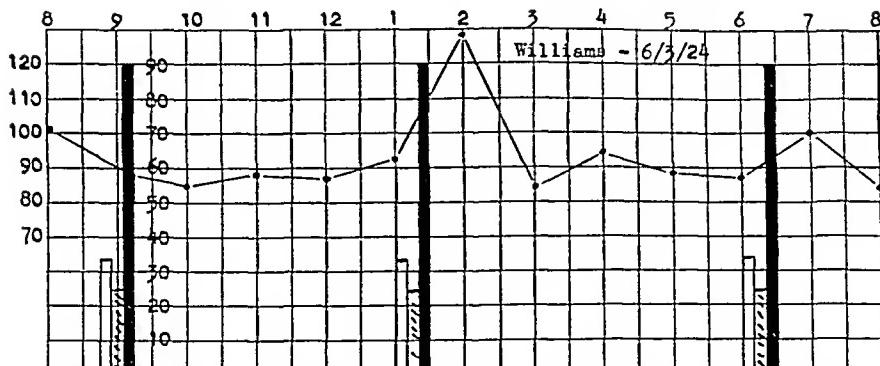


Chart 1—Blood sugar curve in a white man, aged 49, weighing 58 kg, who entered the hospital, April 13, 1924, with typhoid fever, he was fully convalescent, going about the ward and on full diet at the time of the experiment. In this and in the following charts, the abscissas represent time intervals beginning in the forenoon, each space equaling thirty minutes, the figures at the top being hours, the ordinates represent milligrams of blood sugar per hundred cubic centimeters of blood (or thousandths of 1 per cent), each space equaling 10 mg. Such spaces also represent 10 gm of food and 10 units of insulin where these are indicated. The food is presented in grams of protein, fat and carbohydrate, the protein by an open column, the fat by a hatched one, and the carbohydrate by a solid one. In all instances, the time of administration is indicated by the left border of the protein column, the insulin, by a narrow, solid, perpendicular line, and chart numbers correspond to the curve numbers in the text.

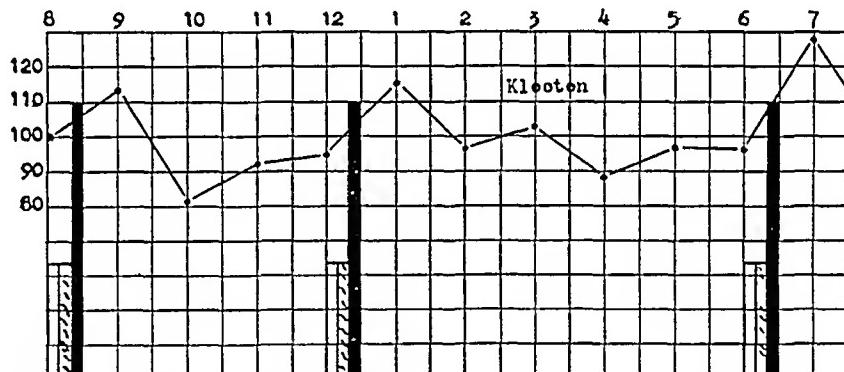


Chart 2—Blood sugar curve in a white man, aged 35, weighing 52.5 kg, confined in the hospital from July 16 to Aug 6, 1924, diagnosis, gastric neurosis (hyperacidity).

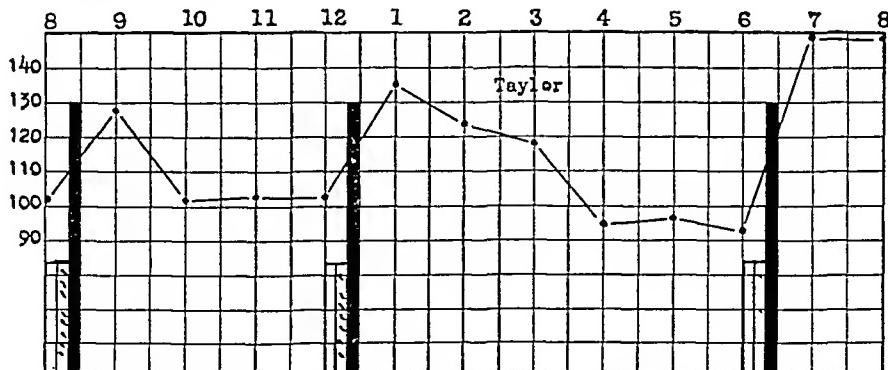


Chart 3—Blood sugar curve in a white man, aged 63, weighing 50 kg, confined in the hospital from July 16 to Aug 2, 1924, diagnosis, arthritis deformans. He had had symptoms for two years. There was slight secondary anemia.

restriction alone. It will be noted that in Cases 7 and 8, the fasting blood sugar levels were somewhat high (0.145 and 0.147 per cent) while in Case 9, the value was only 0.100 per cent. The former two present a type of curve that we have found common to most diabetic

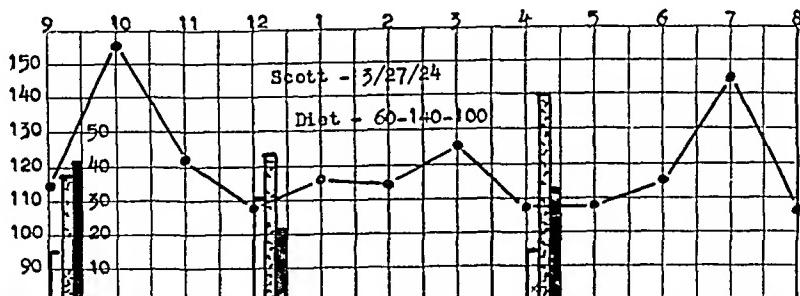


Chart 4—Blood sugar curve in a white man, aged 29, weighing 57 kg, who was convalescent from lobar pneumonia, and in a good general condition

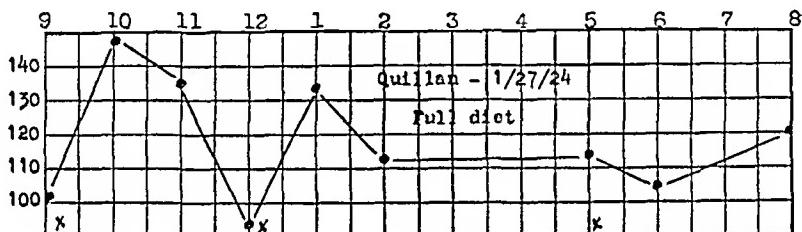


Chart 5—Blood sugar curve in a white man, aged 43, weighing 67 kg, who entered the hospital, Jan 12, 1924, diagnosis, chronic appendicitis. X indicates full house diet consisting of, approximately, 90 gm of protein, 70 gm of fat and 200 gm of carbohydrate

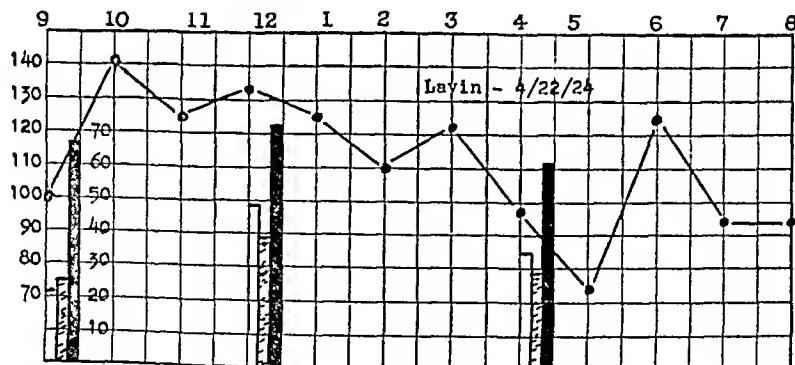


Chart 6—Blood sugar curve in a white girl, aged 19, weighing 62 kg, who entered the hospital, April 7, 1924, because of pain in right hip and thigh, diagnosis, myositis

patients, in that the high points occur after the first and last meals of the day, the highest after breakfast, there being only an insignificant rise after the midday meal. This is seen in only one of our nondiabetic patients (Chart 4). Both these curves are on a higher level throughout

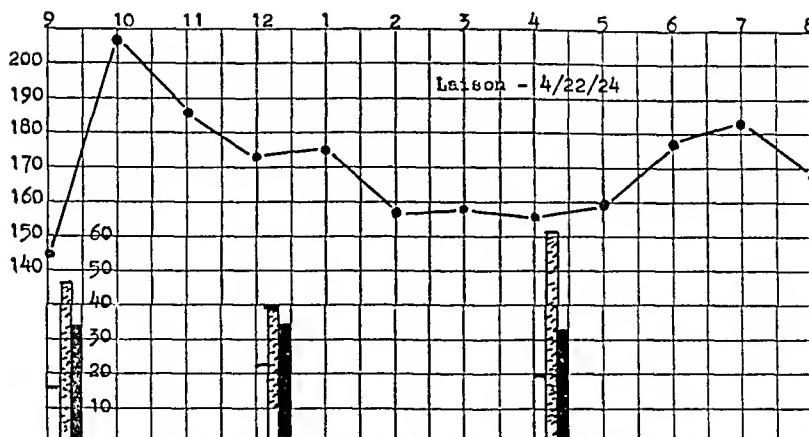


Chart 7—Blood sugar curve in a white woman, aged 45, weighing 64 kg, who had had symptoms for several years. She entered the hospital, March 28, 1924, showing glycosuria, no ketonuria, and a fasting blood sugar of 0.187 per cent. No insulin had been given.

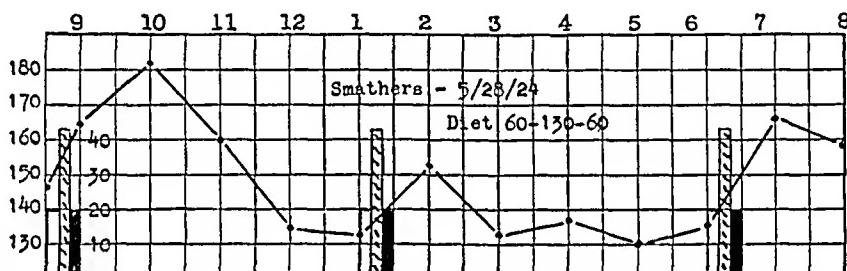


Chart 8—Blood sugar curve in a white man, aged 65, weighing 106 kg, who had had symptoms for five years. He was admitted to the hospital, March 27, 1924, at which time he showed glycosuria, no ketonuria, a fasting blood sugar concentration of 0.268 per cent, and a plasma carbon dioxid content of 55 per cent by volume. Insulin therapy was begun April 1, but had been stopped before this experiment was made. Later, as the diet was increased, insulin had to be resumed.

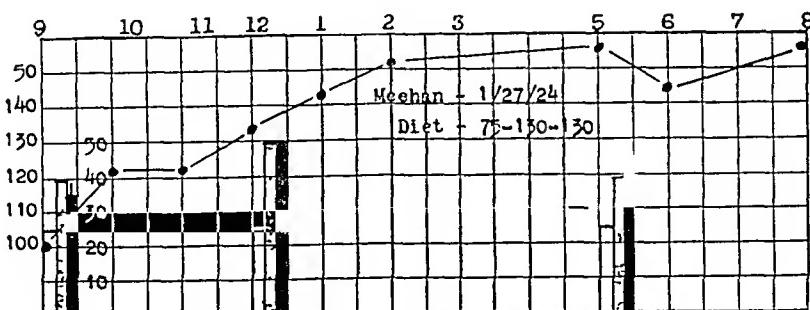


Chart 9—Blood sugar curve in a white man, aged 55, weighing 75 kg, who had had symptoms for five years. He was admitted, Jan 10, 1924, showing a trace of sugar in the urine, no diacetic acid, and a fasting blood sugar of 0.130 per cent. No insulin had been given.

the day than those of our nondiabetic patients. In these cases, the carbohydrate in the diet was equally divided among the three meals, though the fat content in Case 7 was increased in the evening. In Case 9, the curve is different, being only slightly elevated after the morning meal, and steadily rising throughout the rest of the day, but here the carbohydrate fraction of the diet was greater at the two later meals. The diets in all of these cases were fairly adequate, and yet in Cases 7 and 8, the blood sugar concentration exceeded the accepted threshold value for glycosuria (0.170 per cent) only after breakfast. It would seem, therefore, that these were suitable cases for a small dose of insulin in the early morning.

Patients With Severe Diabetes Without Insulin.—The patients whose curves are presented in Charts 10 and 11 may reasonably be considered severe, or potentially severe, diabetic ones since their fasting blood sugar concentrations at the time of admission were 0.288 and 0.300 per cent, respectively, in spite of the fact that neither showed ketonuria. The absence of the latter was undoubtedly due to the fact that both had been carefully dieted before admission to the hospital. Their curves resemble in type those of our milder Cases 7 and 8, though at a decidedly higher level. The high points reached after breakfast and supper are striking, particularly in Case 11. It is true that the carbohydrate factor in the lunch of this patient was reduced to about one-half that of the breakfast, whereas in Case 10 it was increased, but this, while it would perhaps explain the difference between the after-lunch reaction in these two special cases, would not seem a sufficient explanation for the general type of the curve. This will be discussed later.

Patients with Mild Diabetes with Insulin.—The curves in Charts 12 to 21 have been obtained from mild to fairly severe diabetic patients who were receiving insulin in moderate quantities. The first three cover full twenty-four hour periods, the food intake being the same at each meal and identical for the three patients. The insulin dosage also was the same, 10 units one-half hour before each meal. The effect of the morning insulin dosage was to reduce slightly the blood sugar concentration within the half-hour before breakfast, this reduction being promptly overcome by the food. In Cases 12 and 13, there was a definite rise in the sugar concentration within from one to two hours after each meal, highest in the morning and least marked after the midday meal, as in two of our mild and one of our severe cases without insulin. It is striking that this was not true in Case 14, there occurring only a slight rise after breakfast and then a steady drop throughout the day, in spite of food. This result aroused our interest, and we requested roentgenologic study of the gastro-intestinal tract of this patient to

determine if there was any indication of delayed emptying of the stomach which might account for delayed absorption. We were surprised to receive a report to the effect that the patient had evidence of some foreign substances in the stomach, possibly benign tumors, and that these did interfere with gastric evacuation.

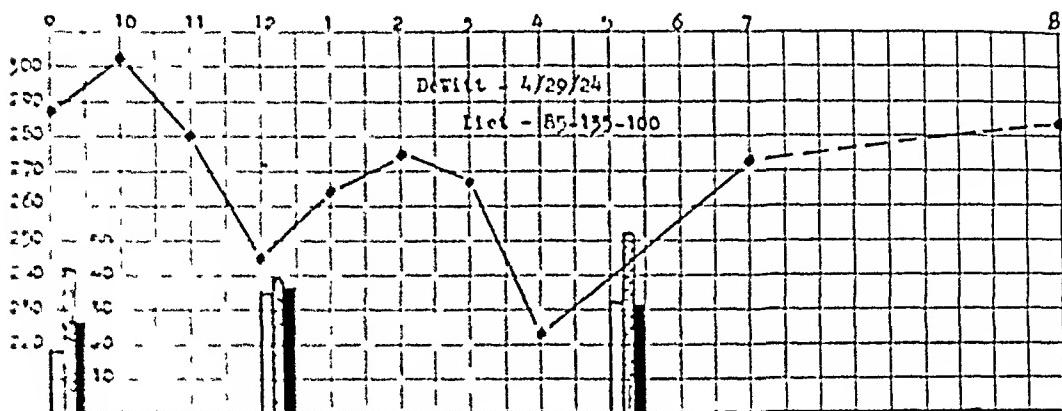


Chart 10.—Blood sugar curve in a white man, aged 56, weighing 74 kg, on diet of acetone, etc. He had shown a tendency to glycosuria for seven years, which was controlled most of that time by careful dieting. He had received no insulin. On his admission to the hospital, April 28, 1924 the urine contained 2+ ketone. No ketones and the fasting blood sugar amounted to 0.288 per cent.

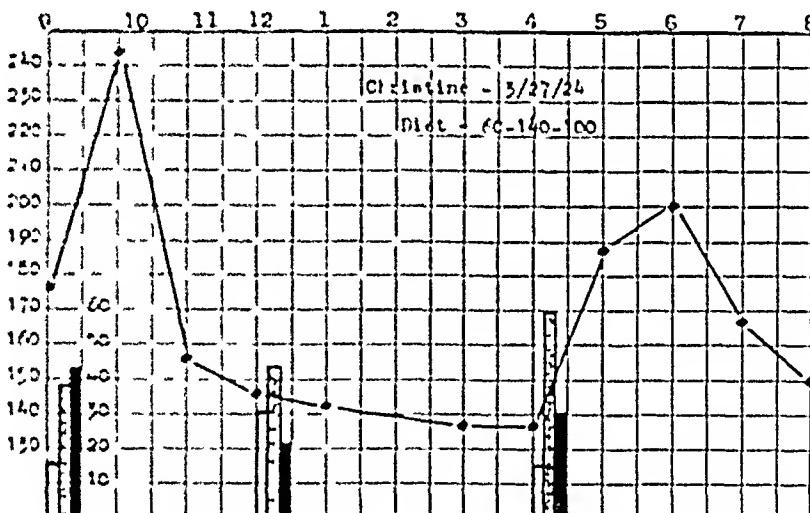


Chart 11.—Blood sugar curve in a white woman, aged 42, weighing 66.5 kg, with symptoms for two years. She entered the hospital, March 3, 1924, at which time she had glycosuria, no ketonuria and a blood sugar of 0.300 per cent. Insulin was begun, March 15. She was discharged, April 8, aglycosuric, on a diet of 60 gm of protein, 140 gm of fat and 100 gm of carbohydrate, with insulin, 15 units, before breakfast.

These three curves (Charts 12, 13 and 14) were the first ones we made, and the similarity of the gradual rise during the night to practically the fasting level of the previous morning suggested that it was not necessary to follow all our cases throughout the night.

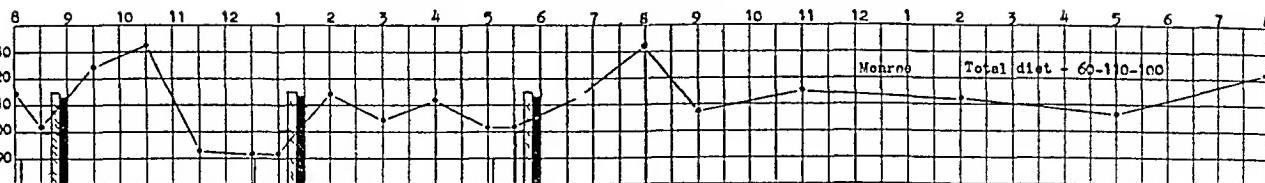


Chart 12—Blood sugar curve in a white man, aged 43, weighing 56 kg, with symptoms for two years He entered the hospital, Oct 29, 1923, showing sugar but no ketones in the urine, a fasting blood sugar of 0.169 per cent, and a plasma carbon dioxid content of 62 per cent by volume Insulin was begun, November 10 He was discharged, November 30, showing no sugar or ketones in the urine, on a diet of 60 gm of protein, 125 gm of fat, 125 gm of carbohydrate and 10 units of insulin before each meal

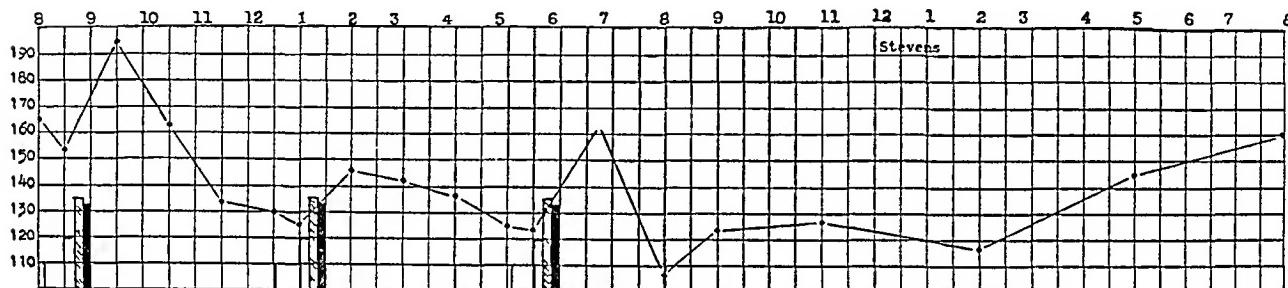


Chart 13—Blood sugar curve in a white man, aged 23, weighing 50 kg, with symptoms of four and one-half years' duration He entered the hospital, Nov 7, 1923, showing glycosuria, ketonuria, a fasting blood sugar of 0.244 per cent and a plasma carbon dioxid content of 30 per cent by volume Insulin was begun on the second day He was discharged, December 12, showing no sugar or ketones in the urine on a diet of 60 gm of protein, 150 gm of fat and 150 gm of carbohydrate, while taking insulin, 10 units, before each meal

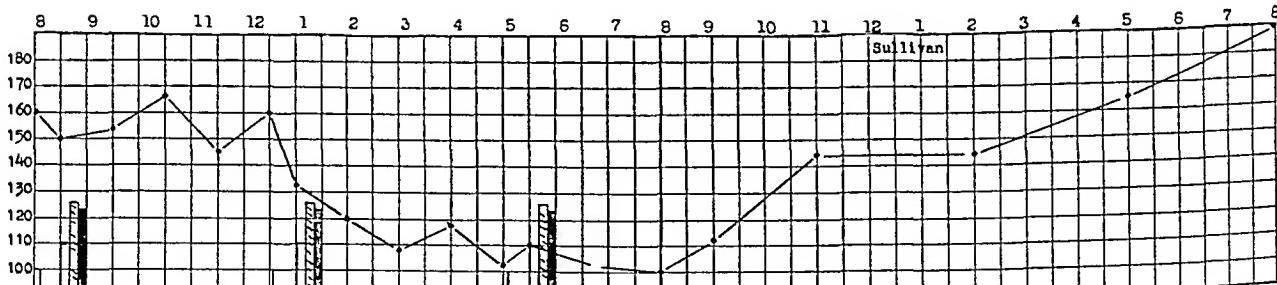


Chart 14—Blood sugar curve in a white man, aged 54, weighing 55 kg, who had had recognized diabetes for eight years He entered the hospital, Nov 9, 1923, showing glycosuria, no ketonuria, a fasting blood sugar of 0.268 per cent and a plasma carbon dioxid content of 58 per cent by volume Insulin therapy was begun, November 15 He was discharged, November 30, without sugar or ketones in the urine, on a diet of 60 gm of protein, 110 gm of fat and 120 gm of carbohydrate, and taking insulin, 10 units, before each meal

In the next case (Chart 15), only a morning dose of 10 units of insulin was given with the breakfast, and it will be noted that there occurred no rise after the midday meal, but a distinct, though slow, one after the evening meal. The same occurred in Cases 16 and 17, though 20 units of insulin were used. To have prevented the evening rise, a second dose would seem to have been indicated. Consequently, in Case

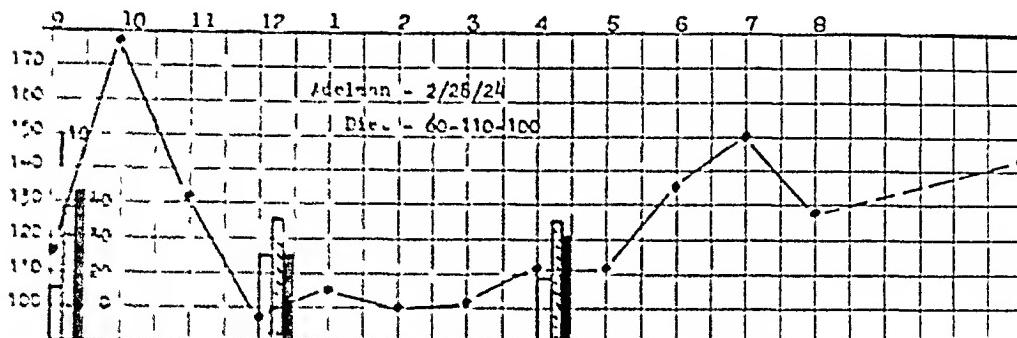


Chart 15.—Blood sugar curve in a white man, aged 52, weighing 83 kg, with symptoms for eight years. He entered the hospital, Feb 9, 1924, showing glycosuria, no ketonuria and a fasting blood sugar of 0.206 per cent. Insulin was given February 21. He was discharged, March 3, sugar free, on a diet of 60, 110, 100 gm of protein, 110 gm of fat and 100 gm of carbohydrate, with 10 units of insulin before breakfast.

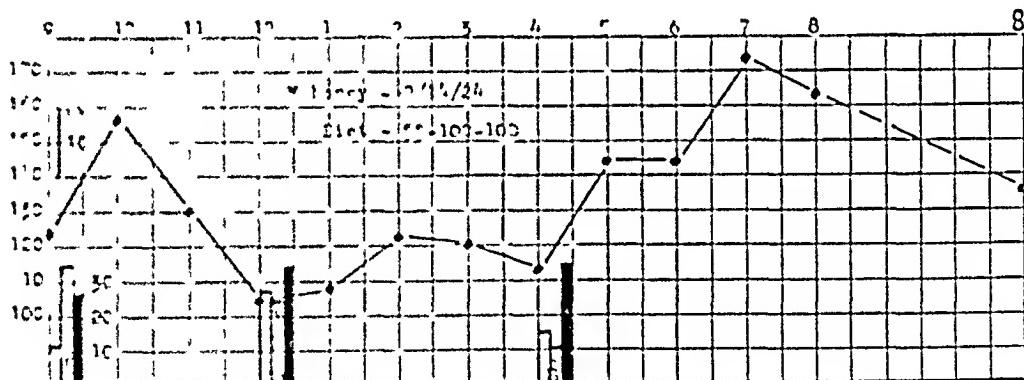


Chart 16.—Blood sugar in a white woman, aged 38, weighing 94 kg, with symptoms for one year. She entered the hospital, January 27, at which time she had a fasting blood sugar of 0.221 per cent and a plasma carbon dioxide content of 67 per cent by volume, but no glycosuria on a full diet. No insulin had been used.

18, somewhat more severe, we gave, in addition to 20 units of insulin in the morning, an evening dose of 10 units. There resulted no sharp rise in the evening curve, but a steady one, over four hours, to a point slightly higher than the morning level, and this occurred in spite of a reduction in the amount of carbohydrate at the supper. This second dose should, therefore, have been a larger one.

Cases 19 and 20, which were still more severe (fasting levels 0.182 and 0.196 per cent), were given larger morning doses of insulin (25 units) but, at the same time, more carbohydrate (65 gm each) at breakfast, and the insulin was given half an hour before the food. In

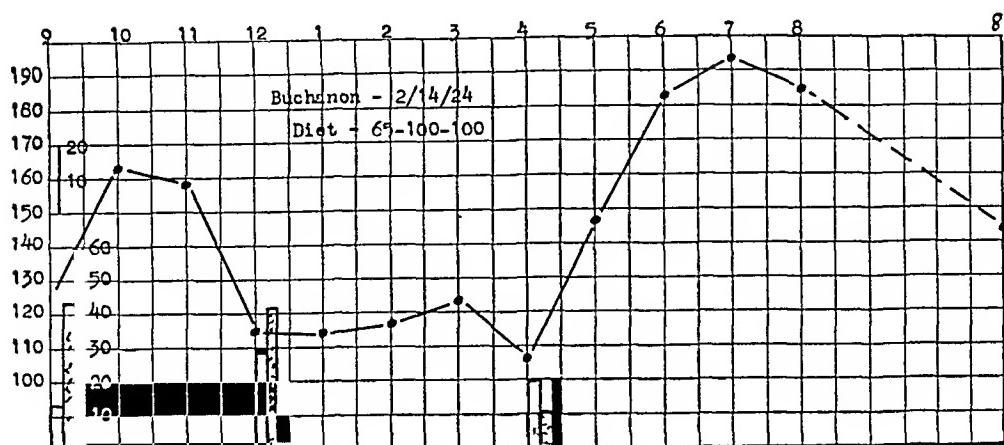


Chart 17—Blood sugar curve in a white woman, aged 50, weighing 68.5 kg, with symptoms for two years. She entered the hospital, Jan 16, 1924, at which time she had glycosuria, no ketonuria, a fasting sugar reading of 0.224 per cent, and a plasma carbon dioxide content of 65 per cent by volume. Insulin was begun one week later. She was discharged February 16, sugar free on insulin, 10 units, twice daily, and a diet of 60 gm of protein, 135 gm of fat and 120 gm of carbohydrate.

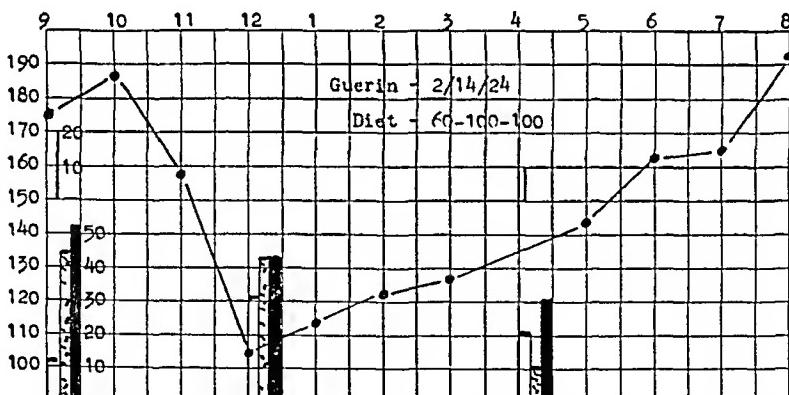


Chart 18—Blood sugar curve in a white woman, aged 67, weighing 71 kg, with symptoms for twelve years. She entered the hospital, Dec 18, 1923, because of gangrene of the toe, at which time she had glycosuria, no diacetic acid, a fasting blood sugar of 0.208 per cent, and a plasma carbon dioxide content of 56 per cent by volume. She had been untreated until admission. Insulin therapy was begun, December 20.

neither of these did the rise in the sugar concentration after breakfast reach the fasting level, thus suggesting an advantage in giving the insulin a short time before the meal. Here, again, it will be noted that there occurred no rise immediately following the luncheon, though no special

significance can be attached to this in these two instances, since the carbohydrate factor in the midday meal was relatively small. Later in the afternoon, there was a distinct rise, so another dose of insulin was indicated before supper.

The curve in Chart 21 is from a fairly severe diabetic patient who had been improving steadily under insulin. It was planned to give him

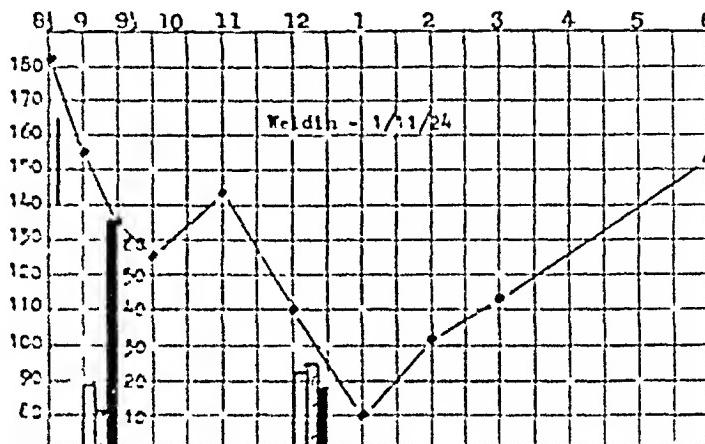


Chart 19.—Blood sugar curve in a white man, aged 34, weighing 43 kg., with symptoms for four months. He entered the hospital, Dec 30, 1923, at which time he showed glycosuria, ketonuria, a fasting blood sugar of 0.345 per cent and a plasma carbon dioxide content of 50 per cent by volume. Insulin was begun Jan. 5, 1924.

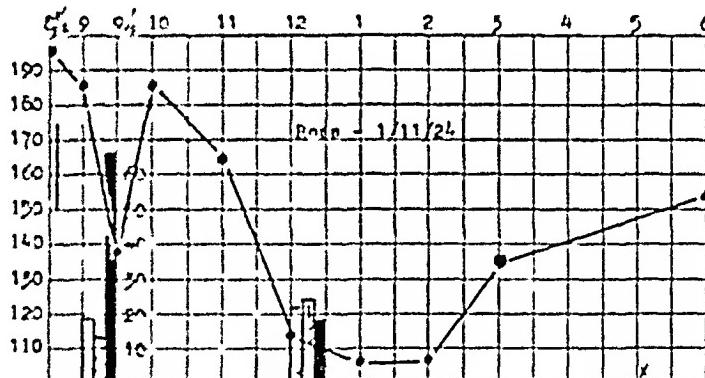


Chart 20.—Blood sugar curve in a white man, aged 39, weighing 57 kg., with symptoms for two years. He had had furuncles for three weeks before admission. He entered the hospital, Dec 9, 1923, at which time he was glycosuric, ketonuric, and had a fasting blood sugar reading of 0.283 per cent and a plasma carbon dioxide content of 31 per cent by volume. Insulin therapy was begun on the second day. He was discharged, Jan 20, 1924, with no sugar or diabetic acid in the urine and on a diet of 55 gm of protein, 170 gm of fat, 80 gm of carbohydrate, and 30 units of insulin before breakfast.

only 15 units the day of our experiment, but by mistake he received 40 units. We therefore increased his carbohydrate, a half-hour later to 50 gm (twice the amount it had been intended he should have), and gave the same amount at luncheon, thus securing the very satisfactory curve which is presented.

In reviewing this group, it will be observed that when the insulin was given at the same time as the breakfast, a rise in the blood sugar concentration developed after this meal. Even when only 10 gm of carbohydrate was given with 40 units of insulin, as in Case 21, there occurred no immediate fall, and a moderate rise after the regular breakfast, thirty minutes later. In those, however, in which the insulin was given alone one-half hour before breakfast, a prompt decline in the blood sugar value developed, and the peak of the rise which followed the meal was usually below the fasting level. Thus, it would seem clear that to avoid the excessive hyperglycemia incident to the first meal of the day in these mild cases, the insulin should be given at least thirty minutes before the food.

Patients with Severe Diabetes with Insulin.—It is not so satisfying to present the remaining cases, those of severe diabetes with insulin, because a practical method of securing curves approaching the normal,

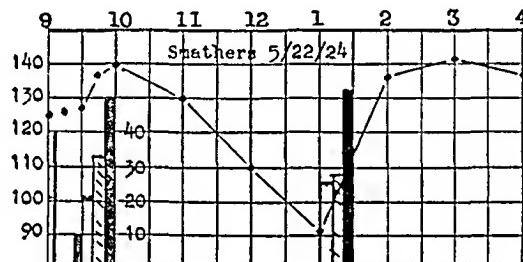


Chart 21.—Blood sugar curve in a white man, aged 25, weighing 106 kg., with symptoms for five years. He entered the hospital, March 27, 1924, at which time he showed glycosuria, no ketonuria, a fasting blood sugar of 0.268 per cent, and a plasma carbon dioxide content of 55 per cent by volume. Insulin therapy was begun, April 1. He was discharged, May 29, sugar free, taking a diet of 55 gm of protein, 160 gm of fat and 80 gm of carbohydrate, with no insulin.

in a routine manner, has not been evolved. We feel, however, that our curves are enlightening and may eventually lead to more satisfactory results.

In certain cases of this group, only one large daily dose of insulin was given in an attempt to determine if it were possible to treat efficiently these patients with the one dose a day, this was given immediately before breakfast, and most of the carbohydrate allowed for the day was given at that meal. Chart 22 shows two curves of a patient who was being managed in this way, with an interval of one week between them. Only a morning dose of insulin was given each day, 35 units the first time and 40 the second, and it was administered immediately before breakfast. The improvement that occurred during the week, as shown in the general level of the curves, is manifest. The fasting levels were not exceeded during the twenty-four hours, and there was no rise after the

first two meals of the day. After the supper, there occurred a steady rise until the following morning. The curve from Case 23 shows the same features. In another patient (Charts 24 and 25) the curves, with an interval of a week between them, show similar characteristics, including a great improvement in the general level during the week, but in these there developed a rise after breakfast. In view of our results in the milder cases, it was thought that, had the insulin in this instance been given from a half to an hour earlier, this postbreakfast rise might

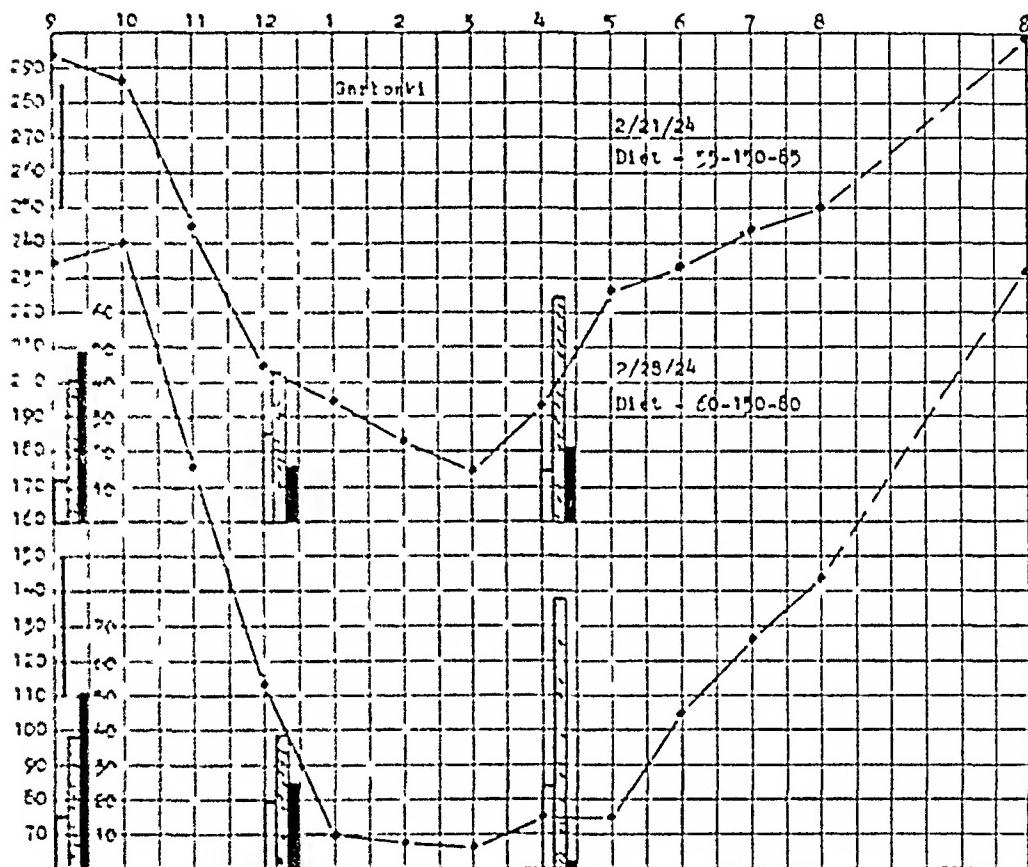


Chart 22—Blood sugar curve in a white man, aged 32, weighing 55 kg, with symptoms for one year. He entered the hospital, Feb 1, 1924, at which time he had glycosuria, ketonuria, a fasting blood sugar of 0.332 per cent, and a plasma carbon dioxide content of 45 per cent by volume. Insulin was begun February 5.

have been avoided. Even such timing of the insulin dosage is not always sufficient to overcome the rise, however, as is illustrated by Case 25 (Charts 26 and 27). On the other hand, the insulin (40 units) was given to another patient (Chart 28) a half-hour before breakfast, and the subsequent rise was eliminated. So it would seem impossible, in the individual severe case, to predict whether or not a dose of insulin which is sufficient to bring the sugar concentration down to a reasonably

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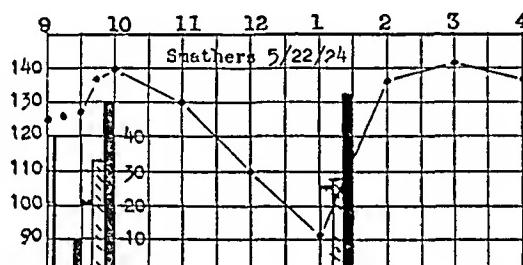


Chart 21.—Blood sugar curve in a white man, aged 25, weighing 106 kg., with symptoms for five years. He entered the hospital, March 27, 1924, at which time he showed glycosuria, no ketonuria, a fasting blood sugar of 0.268 per cent, and a plasma carbon dioxide content of 55 per cent by volume. Insulin therapy was begun, April 1. He was discharged, May 29, sugar free, taking a diet of 55 gm of protein, 160 gm of fat and 80 gm of carbohydrate, with no insulin.

in a routine manner, has not been evolved. We feel, however, that our curves are enlightening and may eventually lead to more satisfactory results.

In certain cases of this group, only one large daily dose of insulin was given in an attempt to determine if it were possible to treat efficiently these patients with the one dose a day; this was given immediately before breakfast, and most of the carbohydrate allowed for the day was given at that meal. Chart 22 shows two curves of a patient who was being managed in this way, with an interval of one week between them. Only a morning dose of insulin was given each day, 35 units the first time and 40 the second, and it was administered immediately before breakfast. The improvement that occurred during the week, as shown in the general level of the curves, is manifest. The fasting levels were not exceeded during the twenty-four hours, and there was no rise after the

first two meals of the day. After the supper, there occurred a steady rise until the following morning. The curve from Case 23 shows the same features. In another patient (Charts 24 and 25) the curves, with an interval of a week between them, show similar characteristics, including a great improvement in the general level during the week, but in these there developed a rise after breakfast. In view of our results in the milder cases, it was thought that, had the insulin in this instance been given from a half to an hour earlier, this postbreakfast rise might

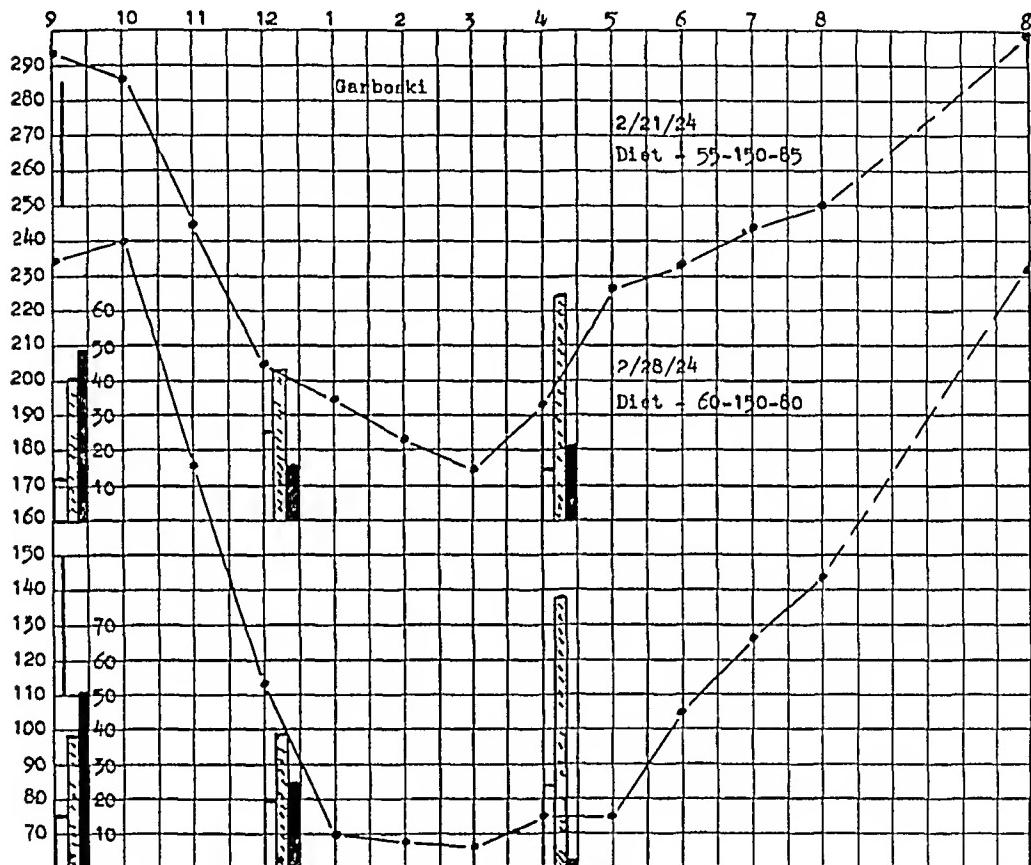


Chart 22—Blood sugar curve in a white man, aged 32, weighing 55 kg, with symptoms for one year. He entered the hospital, Feb 1, 1924, at which time he had glycosuria, ketonuria, a fasting blood sugar of 0.332 per cent, and a plasma carbon dioxide content of 45 per cent by volume. Insulin was begun February 5.

have been avoided. Even such timing of the insulin dosage is not always sufficient to overcome the rise, however, as is illustrated by Case 25 (Charts 26 and 27). On the other hand, the insulin (40 units) was given to another patient (Chart 28) a half-hour before breakfast, and the subsequent rise was eliminated. So it would seem impossible, in the individual severe case, to predict whether or not a dose of insulin which is sufficient to bring the sugar concentration down to a reasonably

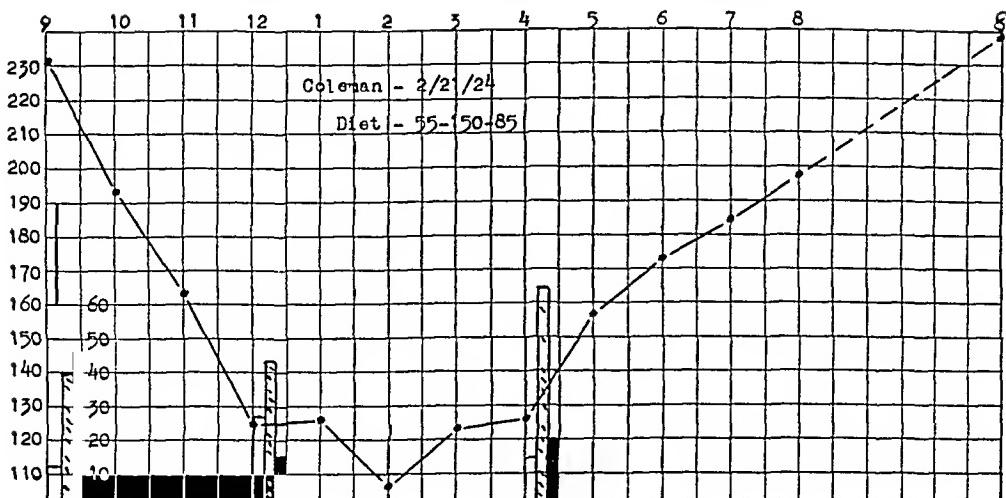


Chart 23.—Blood sugar curve in a white man, aged 32, weighing 43.7 kg, with symptoms for five months. He entered the hospital, Feb 6, 1924, at which time he had glycosuria, ketonuria, a fasting blood sugar of 0.210 per cent, and a plasma carbon dioxid content of 39 per cent by volume. He had numerous furuncles. Insulin was begun three days after admission. He was discharged, February 25, aglycosuric on a diet of 55 gm of protein, 150 gm of fat, and 80 gm of carbohydrate, with insulin, 30 units before breakfast and 10 units before supper.

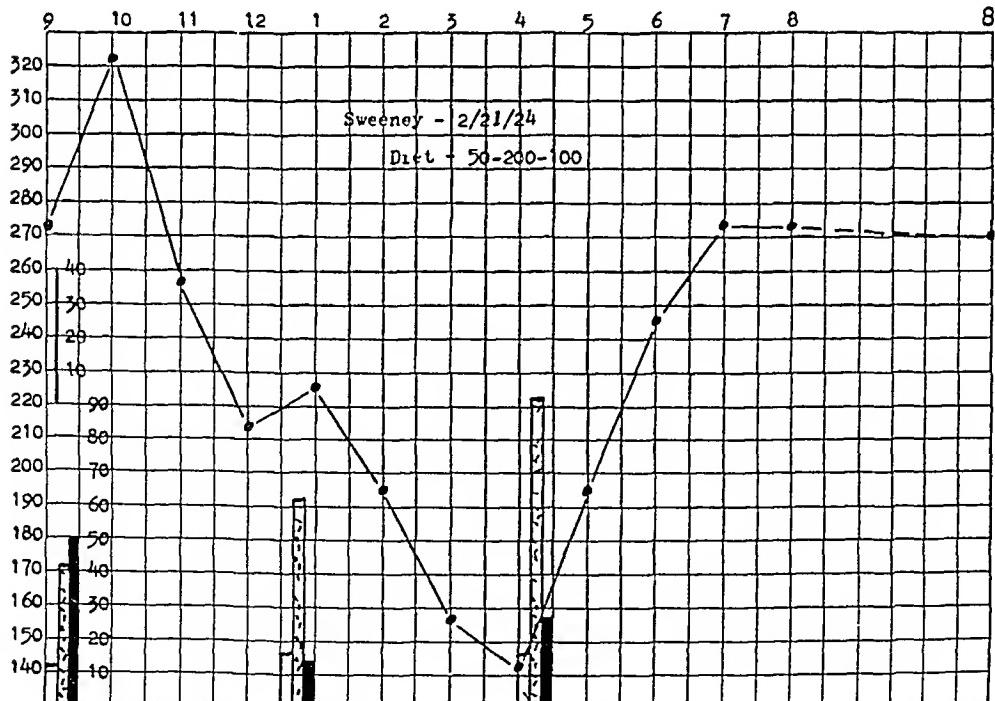


Chart 24.—Blood sugar curve in a white man, aged 36, weighing 52 kg, with symptoms for fourteen months. He entered the hospital, Feb 7, 1924, at which time he showed glycosuria, a fasting blood sugar of 0.222 per cent and a plasma carbon dioxid content of 57 per cent by volume. He had taken insulin before admission.

low level by the middle of the day will prevent a rise within an hour after breakfast, be it given immediately before or from a half to one hour before the first meal of the day. It seems justifiable, however, in

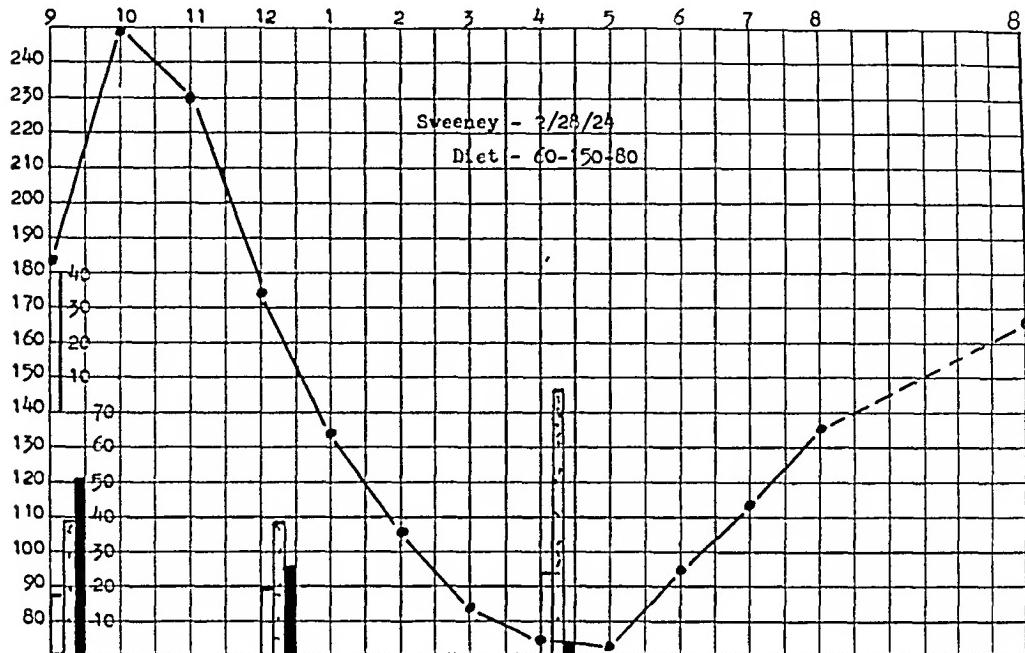


Chart 25—Blood sugar curve in same patient as Chart 24, improvement in general level of the curve after the lapse of one week

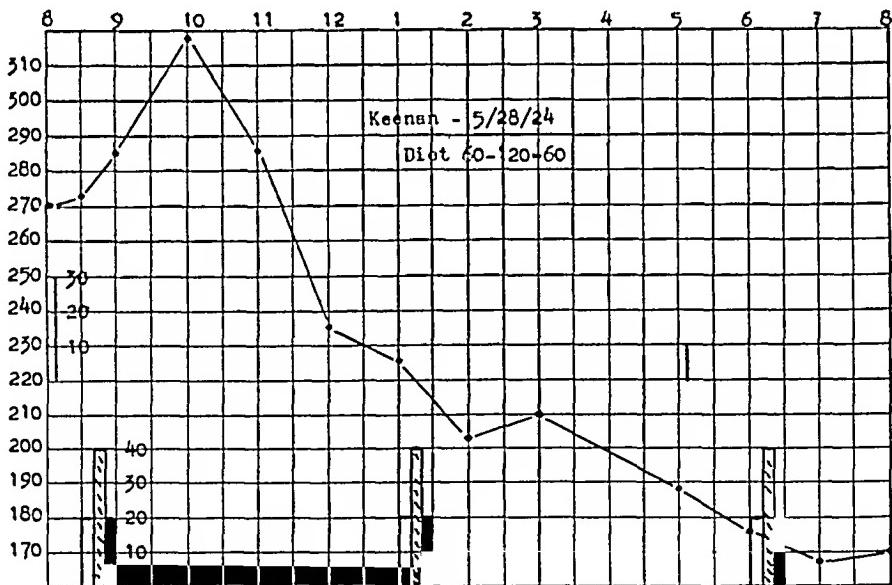


Chart 26—Blood sugar curve in a white woman, aged 53, weighing 54 kg, with symptoms for two years. She entered the hospital, May 6, 1924, at which time she showed glycosuria, no ketonuria and a fasting blood sugar of 0.329 per cent. Insulin was begun May 16.

the light of our experience with the milder cases, to believe that the half to one hour interval between the insulin and the food is more effective in this respect.

In Case 26 (short curve of Chart 28), as well as in Case 21, the experiment was made by giving 10 gm of glucose at the same time as the insulin (40 units) and the regular meal a half-hour later to determine how this might affect the sugar concentration curve. It was thought that, in some

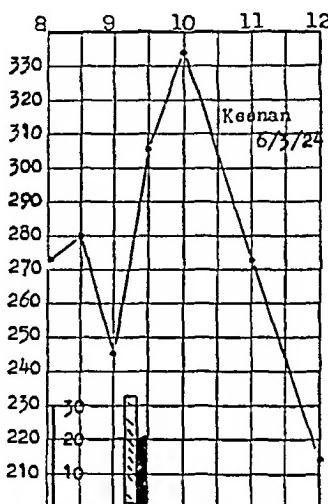


Chart 27—Blood sugar curve in same patient as Chart 26

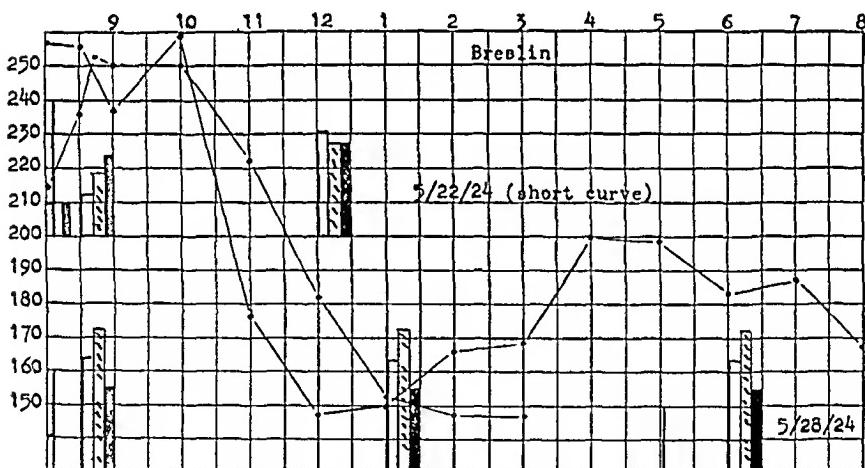


Chart 28—Blood sugar curve in a white man, aged 29, weighing 50 kg, with symptoms for two years. He entered the hospital, May 10, 1924, showing glycosuria, ketonuria, a fasting blood sugar of 0.463 per cent, and a plasma carbon dioxide content of 15 per cent by volume. He left the hospital, against advice, June 7, with a trace of glycosuria, on a diet of 60 gm of protein, 100 gm of fat, and 50 gm of carbohydrate, and insulin, 35 units before breakfast and 25 units before supper.

way, this small amount might initiate the mechanism of glucose disposal and so prevent the excessive rise in blood sugar after the larger amount of carbohydrate given with the breakfast. It will be noted, however, that even this small dose of carbohydrate itself caused a definite rise within thirty minutes, in spite of the large accompanying injection of

insulin, and that in Case 26 the level was still higher fifteen minutes later, after the breakfast had been taken. The uselessness of this procedure is therefore suggested.

The curve of Case 27 (Chart 29) resembles others of this group, except that the second dose of insulin, in the evening, was sufficient to prevent a rise in the level after supper, as it was also in Case 26 (long curve). The morning dose in Case 27, however, was obviously not large enough for the severity of the case and the amount of carbohydrate allowed.

These data show that, in the more severe cases, it is possible to bring the blood sugar level down to a reasonably satisfactory figure by midday and to keep it there during most of the afternoon by giving a large dose of insulin one-half to an hour before breakfast. A second dose in the

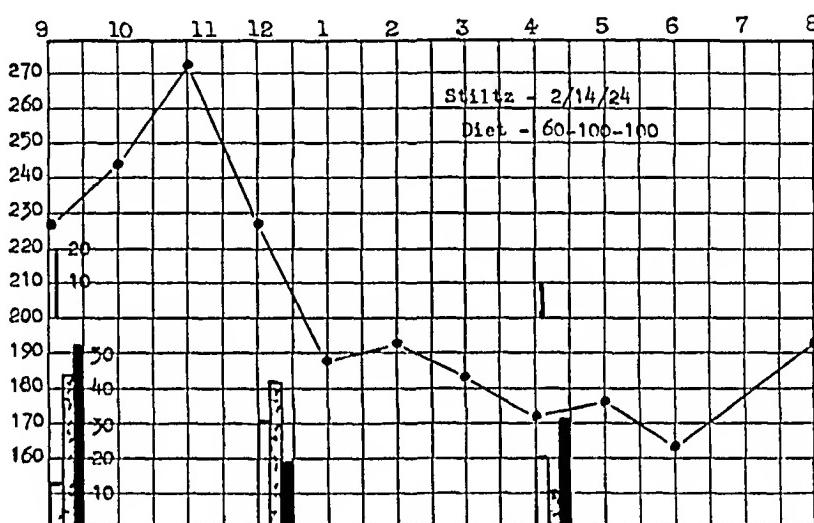


Chart 29—Blood sugar curve in a white woman, aged 62, weighing 44 kg, with symptoms for six years. She entered the hospital, Jan 20, 1924, at which time she showed glycosuria, ketonuria, a fasting blood sugar of 0.440 per cent, and a plasma carbon dioxide content of 35 per cent by volume. Insulin therapy was begun at once. She was discharged, April 6, still showing traces of sugar in the urine, no ketonuria, a fasting blood sugar of 0.300, and a plasma carbon dioxide content of 59 per cent by volume. At this time, she was on a diet of 80 gm of protein, 140 gm of fat and 100 gm of carbohydrate, and getting insulin, 20 units before breakfast and 10 units before supper.

late afternoon, provided it is of sufficient amount, will prevent any marked rise after supper. It was frequently observed, however, that such treatment did not prevent a slow rise during the night to an unsatisfactory level by the following morning.

To overcome this excessive morning concentration, we have, in certain instances, administered a third dose of insulin at midnight, thus giving it at practically eight-hour periods. Charts 30, 31 and 32 show the effects of such timing of the insulin dosages. The curve in Chart 30 was made of a patient who had been showing glycosuria and high morn-

ing fasting figures consistently on a fixed diet and with adequate morning and evening doses of insulin. On the day of the experiment (no insulin having been given during the preceding night), with the same diet and the same two day doses of insulin, a third midnight dose (10 units) was added. It will be observed that, as a result, the concentration on the following morning was only 0.131 per cent, and that the curve was practically flat throughout that night. Chart 31 shows similar features. It is unfortunate that we could not have continued these curves for another twelve hours for comparison with the previous day. If one started with the low morning level, it seems probable that a very satisfactory result throughout the twenty-four hours would

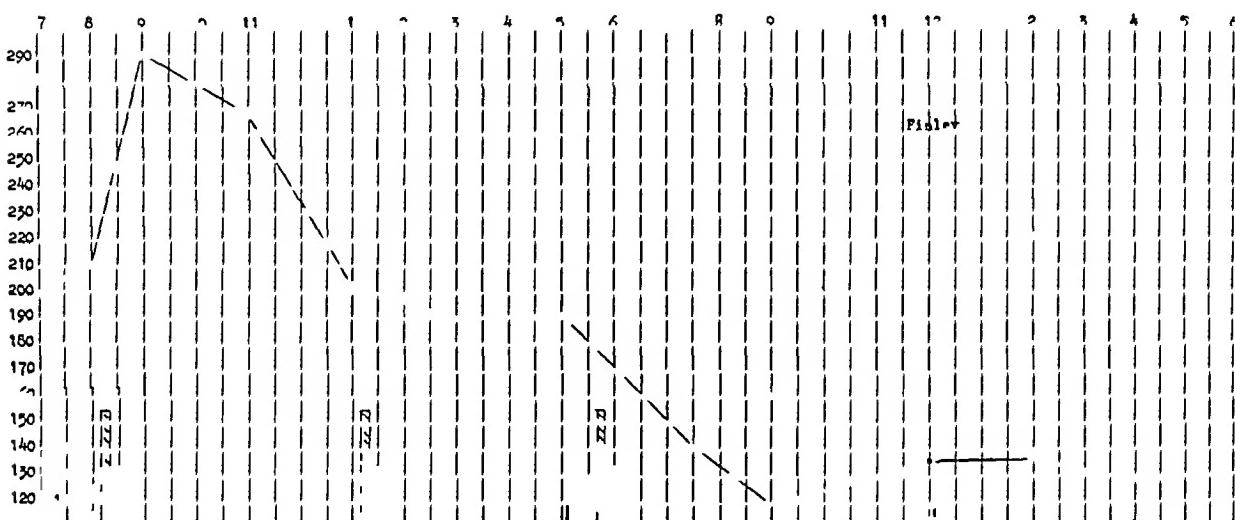


Chart 30—Blood sugar curve in a white woman, aged 70, weighing 55 kg, with diabetes of five years' duration. She was admitted, June 3, 1924, with glycosuria, mild ketonuria, a blood sugar of 0.352 per cent, and a plasma carbon dioxide content of 53 per cent by volume. Insulin therapy was begun, June 9. She was discharged, July 16, at which time she was taking 60 gm of protein, 130 gm of fat, 70 gm of carbohydrate, and 30 units of insulin before breakfast, 10 before supper and 10 at midnight. On this regimen, she became free of ketones and sugar in the urine, and had a fasting blood sugar of 0.122 per cent.

have been obtained. This is proved, apparently, by the fact that the patients on this regimen became free of sugar in the urine. There were at no time any symptoms of hypoglycemia.

Finally, a curve was obtained from another patient (Chart 32) who had been on three doses of insulin daily, so timed, for a week, and who in consequence had become aglycosuric. On admission to the hospital, she was practically in diabetic coma. A few days later, her fasting blood sugar level was 0.262 per cent, and the peak of the rise, after breakfast, with a preceding dose of 25 units of insulin, was 0.327 per

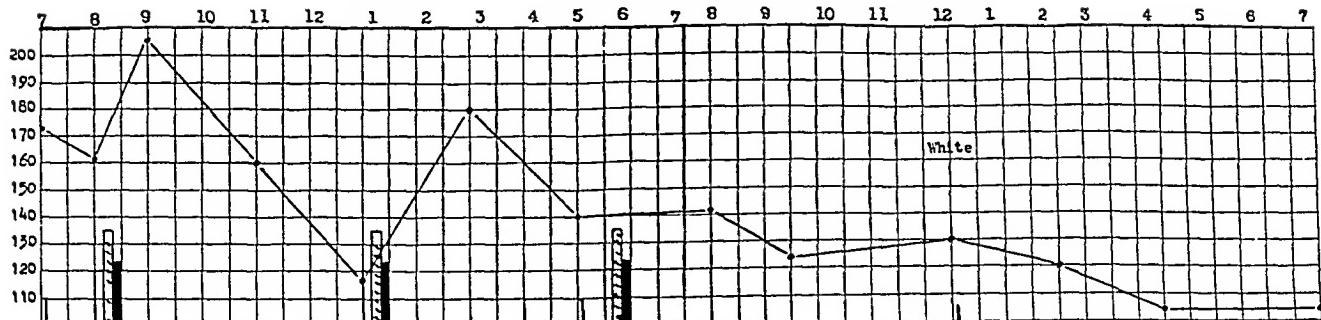


Chart 31—Blood sugar curves in a white man, aged 57, weighing 49 kg, with symptoms for ten months. The Wassermann reaction was positive. On admission to the hospital, the urine showed sugar, acetone and diacetic acid, the blood sugar was 0.232 per cent, and the plasma carbon dioxid content, 40 per cent by volume. With three doses of insulin daily, as shown in this chart, the urine became sugar free, and later continued to be sugar free on two doses daily, 15 units before breakfast and 10 before supper. On discharge, the fasting blood sugar level was 0.115 per cent.

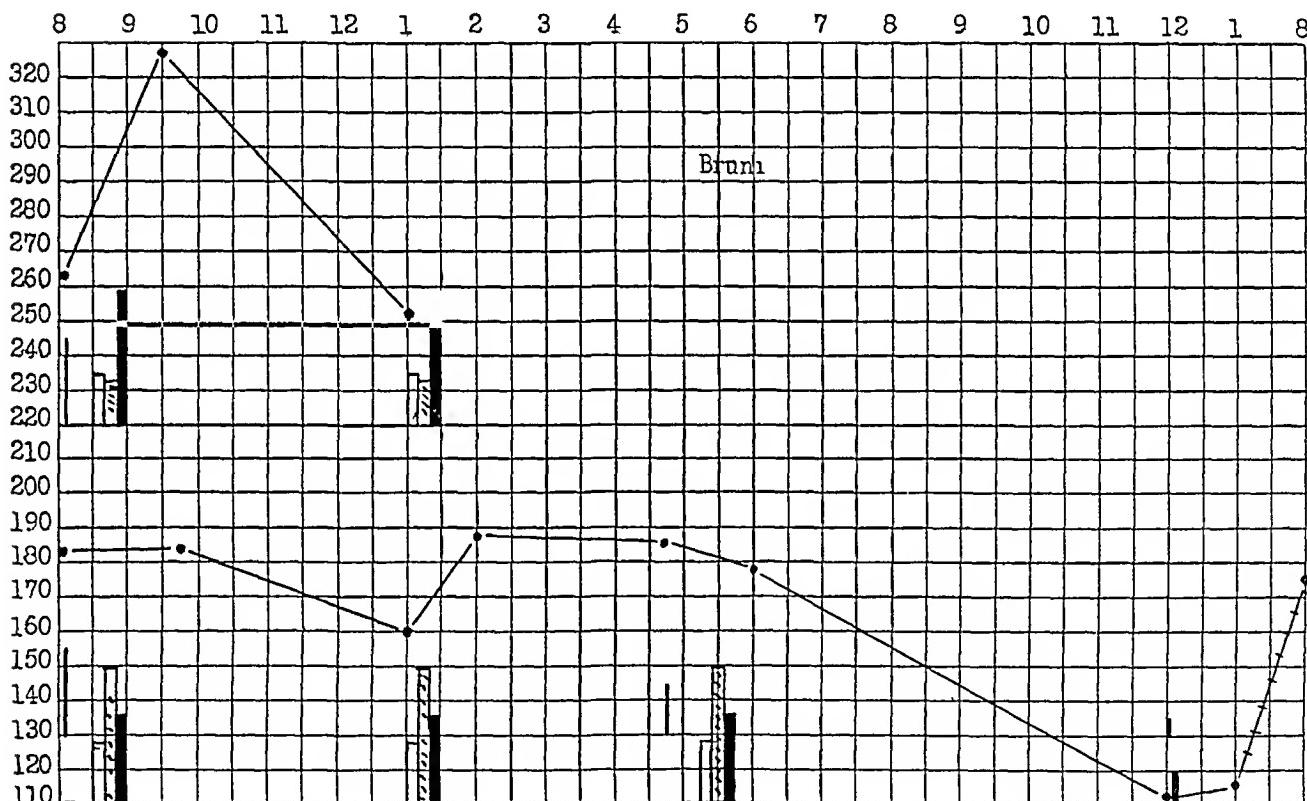


Chart 32—Blood sugar curve in a white woman, aged 34, weighing 53 kg, with symptoms of diabetes for four years. She was treated in several hospitals, and had had insulin for a time, but had stopped it before admission to the University Hospital. On admission, she was practically in coma, though slightly responsive to commands. She had a blood sugar concentration of 0.548 per cent and a plasma carbon dioxid content of 7 per cent by volume. Ketonuria was marked. She came out of coma after the administration of 180 units of insulin and glucose, intravenously, during the first twenty-four hours. Three days later, when on diet of 45 gm of protein, 35 gm of fat, 115 gm of carbohydrate and insulin, 60 units, the curve in the upper part of the chart was made. A week later, the lower curve was made. She was then entirely free of both sugar and ketones in the urine.

cent (upper curve in Chart 32) At this time, we began to give 10 units of insulin at midnight, without any food, later increasing the dosage to 15 units Then he became sleepless, had a little sweating and a sensation of hunger To overcome these symptoms, 10 gm of carbohydrate were given at the same time as the night insulin, and, finally, the latter was reduced to 5 units, but the carbohydrate feeding was continued The hypoglycemic manifestations were in this way promptly controlled The curve presented shows no excessive hyperglycemia on a diet containing 50 gm of protein, 115 gm of fat and 110 gm of carbohydrate At the same time, she was getting a total of only 45 units of insulin 25 units a half-hour before breakfast, 15 units a half-hour before supper, and 5 units at midnight The lowest blood sugar value (0.112 per cent) was present at midnight, suggesting that the dose of insulin before supper might safely have been somewhat reduced We have not obtained such a marked reduction in the fasting blood sugar level so quickly without the use of insulin during the night

COMMENT

The response of the human organism to the ingestion of a single dose of carbohydrate, as determined by the sugar concentration of the blood for from two to four hours afterward, has been extensively studied in both normal and diabetic subjects, but sufficient attention has not been directed to the reaction that follows repeated meals of mixed composition throughout full day periods Such studies are of great practical importance in connection with the administration of insulin to patients with diabetes

It is of course fully appreciated that ordinarily, unless insulin has been administered beforehand, a rise in the blood sugar level follows every meal containing carbohydrate That diets free of carbohydrate have no such effect in normal persons is also understood This has been demonstrated by several investigators, among them Mosenthal, Clausen and Hiller,³ who showed, however, that in patients with mild diabetes there sometimes occurred a slight rise after meals containing only very small amounts of carbohydrate These aspects of the problem have not been touched on in our work, neither have we studied the effects of insulin alone, without food, on the blood sugar concentration, because this has been adequately presented by Banting, Best, Collip, Campbell and Fletcher⁴ and by Fletcher and Campbell⁵ Their curves

3 Mosenthal, H. O., Clausen, S. W., and Hiller, A. The Effect of Diet on Blood Sugar, *Arch. Int. Med.* **21** 93 (Jan.) 1918

4 Banting, F. G., Best, C. H., Collip, J. B., Campbell, W. R., and Fletcher, A. A. Pancreatic Extract in Diabetes, *Canad. M. A. J.* **12** 141-146 (March) 1922

5 Fletcher, A. A., and Campbell, W. R. The Blood Sugar Following Insulin Administration, *J. Metabolic Res.* **2** 637-649 (Nov.-Dec.) 1922

were plotted to show hourly variations in the blood sugar over periods of from four to seven hours and the values at less frequent intervals for a longer time. As is now well known, they found a steady fall in the curve, which reached its low point at from two to twelve hours, usually four, and return to the original level at a variable rate. The general effects were found to be the same in nondiabetic patients and in diabetic patients, but there was a tendency for the decline to be dependent on the initial blood sugar concentration, being greater with the higher fasting level.

Our interest has centered mainly on the effects of three meals of mixed composition, on the level of blood sugar throughout the day in diabetic patients, and on the modifying influence of insulin administrations. In our work, it soon became apparent that the effect was not the same for each meal of the day, whether nondiabetic or diabetic patients were being studied, and whether or not insulin was being given. The general tendency, with three meals of equal composition, was for the maximal rise to occur after breakfast. Mosenthal, Clausen and Hiller had noted this in their mild diabetic patients who were on diets largely free of carbohydrate. When large amounts of carbohydrate were given to one of their diabetic patients, however, they got a different result, the blood sugar figures after the noon and evening meals being greater than after breakfast. From this single case, they inferred that the course of events in diabetic patients with a high carbohydrate diet was different. It must be pointed out, however, that the amounts of carbohydrate given at the later meals in their case were greater than the amount given at breakfast (116 and 75 gm as against 45). Our results, as seen in many cases of both mild and severe diabetes in which the patients received the same amount of carbohydrate at each meal, indicate that the maximal rise usually occurs after the breakfast, even when an adequate amount of carbohydrate is allowed. It would seem, therefore, that this holds true for diets either low or reasonably high in carbohydrates.

Hamman and Hirschman⁶ have observed in normal persons that superimposed doses of glucose are not necessarily always followed by a steplike rise in the blood sugar, but frequently by a less marked reaction or none at all, and they concluded from their experiments that the ingestion of glucose in some way stimulated the mechanism of carbohydrate disposal so that the repeated ingestion of the same amount caused a less marked hyperglycemia. Similar results were obtained by

6 Hamman, L., and Hirschman, I. I. Effects Upon the Blood Sugar of the Repeated Ingestion of Glucose, Bull Johns Hopkins Hosp **30** 306 (Oct.) 1919.

MacLean and de Wesselow,⁷ who gave the glucose doses at one and one-half hour intervals. Their curves after the first and the second doses had the same form, but the first one was distinctly more elevated. The explanation they give is that the hyperglycemia resulting from the first dose initiates the glycogen-forming mechanism which causes a fall in the sugar level, and that this mechanism, not having subsided when the second one is given, tends to prevent so marked a blood sugar concentration after that dose. In diabetes, they feel that this mechanism fails in varying degree. Foster⁸ also has presented curves showing a less decided reaction from a second dose of glucose in normal persons, and has adduced evidence that seems very convincing in favor of the theory advanced by MacLean and de Wesselow. This hypothesis has been questioned, however, by Folin and Berglund⁹ who believe that the fall

9 Folin, O., and Berglund, H. Transportation, Retention and Excretion of Carbohydrates, *J Biol Chem* **51** 213-273 (March) 1922
comes when the tissues are well supplied with available food material, and that the lower level is simply an index of the fact that the need for sugar transportation from some tissues to others has temporarily dropped very low or ceased altogether.

Whatever the true explanation may be, our only immediate interest is in the fact that under certain circumstances, in both nondiabetic and diabetic patients, a second dose of carbohydrate, given within a few hours after the first, does not cause such a high blood sugar rise as the former one. This is seen in many of our cases in which no insulin was used (Charts 4, 5, 6, 7, 8, 10 and 11), including both nondiabetic and diabetic. It also occurred in many of the cases in which insulin was given, but in these the insulin itself was probably the main factor.

It seems essential, however, in order to secure this lessened rise after a second dose, that not too long a period elapse between the feedings. MacLean and de Wesselow found that in normal persons an interval of three or four hours was sufficient for the sugar concentration again to reach the fasting level and that the reaction to the second dose was independent of the first one. It may be assumed, according to their theory, that in this length of time the glycogen-forming mechanism subsides. This would seem to explain those of our cases in which the rise after luncheon or the evening meal was equal to or greater than that after breakfast (Charts 1, 2 and 3). Our data would suggest that this subsidence of glycogen formation occurs more readily in the non-diabetic than in the diabetic patient.

7 MacLean, H., and de Wesselow, O. L. V. Estimation of Sugar Tolerance, *Quart J Med* **14** 103 (Jan.) 1921

8 Foster, G. L. Carbohydrate Metabolism, Interpretation of Blood Sugar Phenomena Following Ingestion of Glucose, *J Biol Chem* **55** 303-314 (Feb.) 1923

Our six twelve-hour curves on nondiabetic patients with mixed diets show characteristics that can be reconciled with the foregoing considerations. In practically all, there occurred a rise in the blood sugar level after each meal. When the interval between breakfast and luncheon was only three hours, the rise after the latter meal was less than that after breakfast, but when the interval was four or more hours, the second rise was equal to or greater than the first one. It will be noted that the curves from the patients with mild diabetes have the same general features except that they are consistently on a somewhat higher level. In these especially is the higher after-breakfast portion of the curve interesting, as the sugar concentration often exceeded the threshold value for glycosuria only at that time. This is the justification for the common practice of giving insulin in these mild cases only before the first meal of the day. It is not, as sometimes supposed, because the insulin has an effect throughout the full day. In our more severe cases without insulin (Charts 10 and 11), the sugar concentration is seen to be high in the latter part of the day as well as in the morning, one curve keeping well above the threshold value for glycosuria throughout the day. These patients would necessarily, if kept on the same diets, require an insulin effect continuously.

Our other curves represent experiments with the administration of insulin to diabetic patients in varying stages of the disease. In the beginning (Charts 12, 13 and 14), we followed the Toronto plan of giving it before each meal, believing that it was not effective for more than four hours, on the average, and wishing to supply it at the times that food was being absorbed. It soon became apparent, however, that unnecessarily low blood sugar values in the afternoon were being obtained. One of us (L J¹⁰) showed this in a previous article. It is also to be seen in curves published by Wilder, Boothby, Barborka, Kitchen and Adams,¹¹ by Williams¹² and by others. Consequently, we learned that the midday dose of insulin could well be dispensed with. In all but the very mild cases, however, the dose before supper is clearly indicated, as many of our curves in which this dose was omitted will show (Charts 16, 17, 19, 22, 23 and 24). In certain others, even small doses of insulin in the late afternoon were not sufficient to keep down an evening rise. We also discovered that in many severe cases on which unfortunately we were not able to procure satisfactory curves

10 Jonas, L. A Report of Sixty-Four Cases of Diabetes Mellitus Treated with Insulin, *Am J M Sc* **166** 687-699 (Nov) 1923

11 Wilder, R M, Boothby, William, Barborka, C M, Kitchen, H D, and Adams, S F. Clinical Observations on Insulin, *J Metabolic Res* **2** 701-728 (Nov-Dec) 1922

12 Williams, J R. A Clinical Study of the Effects of Insulin in Severe Diabetes, *J Metabolic Res* **2** 729-751 (Nov-Dec) 1922

for inclusion herein, large doses of insulin before supper did not prevent glycosuria and high blood sugar values in the early morning.

In an effort to overcome this high morning blood sugar, we experimented with a midnight dose of insulin, thus giving these patients three doses a day at approximately eight hour intervals (8 a.m., 5 p.m. and midnight). Knowing that recovery from the effects of the insulin given before supper did not occur until about that time, we did not feel that it was safe to give it earlier. The results from this timing of the insulin dosages have been commented on in connection with the detailed explanation of our curves, and it need only be noted here that Allen and Sherrill¹³ have emphasized the need for an insulin effect continuously in such cases, no matter how the food is administered, in order to care for the glycogen which is constantly being broken down. They favor its administration before each meal and, in certain severe cases, at six hour intervals. Still more recently, Allen¹⁴ has suggested that the last dose for the day be given an hour after supper or at bed-time. Our data, however, indicate the uselessness, and possibly even the harm from hypoglycemia of a midday dose in the ordinary case. When two doses a day, given before breakfast and supper, respectively, do not rid a patient of glycosuria and the morning fasting level remains high, we unhesitatingly favor the extra dose being given late enough in the evening to reduce definitely the early morning value. This, we believe, is much more apt to occur if it is given within at least eight hours of the morning feeding, usually about midnight. Whether or not a small amount of carbohydrate should be given at the same time to overcome the possibility of hypoglycemia within the next hour or two depends on the patient's clinical reaction or on a blood sugar determination made one or two hours after the administration of the insulin. In some cases, we have found it necessary. On the other hand, we now have under observation a woman who has been receiving 15 units each midnight without any food, and at no time has she shown any evidence of hypoglycemia.

If we review all our curves, it will be noted that without insulin the highest blood sugar concentration usually occurs one hour after breakfast and with insulin, either at that same time or just before the administration of the first dose of insulin for the day. They also show that practically the lowest blood sugar level without insulin is to be found just before breakfast and that with insulin as we have used it, the lowest level is just before lunch or in the midafternoon. From this,

13 Allen, F. M., and Sherrill, J. W. Clinical Observations with Insulin, *J. Metabolic Res.* **2** 803-985 (Nov-Dec) 1922.

14 Allen, F. M. Timing of Insulin Doses, *J. A. M. A.* **82** 1937 (June 14) 1924.

follows that the high and the low points in any case may be discovered by making in one day three routine determinations one before breakfast or before the first insulin administration, if that is being used, one an hour after breakfast, and one just before lunch. By means of these three estimations, a reasonably accurate picture of the full day curve can be formed. The upper curve in Chart 32 was so obtained. For practical purposes, these are the only determinations of the blood sugar needed in the ordinary case, though in certain severe ones, it may be helpful to know, in addition, the level in the early evening, an hour after supper, by which the presupper dosage of insulin may be gaged, and the midnight concentration.

Another point of practical importance may be drawn from the fact that in diabetic patients without insulin, the highest blood sugar concentration develops soon after breakfast. If sugar occurs in the urine, it would be expected in greatest amount at the same time. We have repeatedly found this to be true, glycosuria often being present at only this time in the day. In consequence, when only a single specimen of urine can be obtained in suspected cases of diabetes, as often happens in office practice, one voided an hour or more after breakfast should be secured.

SUMMARY AND CONCLUSIONS

1 A series of thirty-four blood sugar concentration curves were made on twenty-nine patients, six nondiabetic and twenty-three diabetic, and covered periods up to 24 hours. This was done in an effort to work out a more satisfactory routine method of regulating the dosage and the time of administration of insulin to diabetic patients.

2 The ideal method was not arrived at, but the following general rules for the management of such cases seem warranted:

(a) With a maintenance diet equally distributed among the three meals of the day, mild cases of diabetes may be kept within the normal limits of glycemia by means of a single dose of insulin administered a half-hour before breakfast.

(b) More severe cases require, in addition to an adequate morning dose, a second but somewhat smaller one a half-hour before the evening meal.

(c) When the morning fasting level of blood sugar cannot be kept below the threshold value for glycosuria by these two doses, a third one is indicated at about midnight.

(d) The amount of insulin to be administered at each time must be determined by blood sugar estimations made before and after the meals.

3 When insulin is not being given and the diet factors are the same for each of the three regular meals, the highest blood sugar concentration occurs usually about one hour after breakfast, and the lowest is before breakfast

4 When insulin is used, as suggested in the foregoing, the highest point may be attained before the first insulin administration of the day or an hour after breakfast, while the lowest point is usually reached just before the midday meal or in the midafternoon

5 For practical purposes, it is suggested that, in the study of all diabetic patients, three blood sugar determinations should be made on one day, one on a specimen collected before the breakfast or before the first administration of insulin, if that is being used, one an hour after the breakfast, and a final one just before the luncheon. By these three estimations a reasonably accurate picture of the full day curve can be formed

6 In all cases of diabetes, the single specimen of urine which is most likely to show sugar is one voided from one to two hours after breakfast

PANCREATIC AND HEPATIC ACTIVITY IN DIABETES MELLITUS

THE ALTERATIONS WITH SOME OBSERVATIONS ON THE
ETIOLOGY OF THE DISEASE *

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A brief preliminary report¹ has already been made of the findings obtained in a study of pancreatic and hepatic activity in cases of diabetes mellitus. It is the purpose of this paper to present these findings in detail and, so far as our findings seem to bear on them, to comment on certain considerations in this disease.

REVIEW OF THE LITERATURE

Although the recent work of Banting² and his collaborators has contributed an invaluable addition to our methods of treating diabetes mellitus, there still remains much to be desired in our knowledge of the actual etiology of this disease. That a deficiency of the internal secretion of the pancreas is the immediate cause of the glycosuria is uncontestedly proved, but the extent to which other organic functions are involved still remains a question. According to Allen,³ in most, if not in all, cases of diabetes mellitus there must have been a preceding disease of the pancreas. This investigator believes that such pancreatic disease usually involves damage to both the insular and acinous cells. According to Joslin,⁴ although proof for the cause of the disease is still lacking, "an antecedent pancreatitis would appear to be the most

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This paper is No 28 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Disease.

1 Jones, C. M. Alterations in Liver Function and in the External Secretory Activity of the Pancreas in Diabetes Mellitus. A Preliminary Report, Boston M & S J 189 851 (Nov 29) 1923

2 Banting, F. G., and Best, C. H. The Internal Secretion of the Pancreas, J Lab & Clin Med 7 251 (Feb) 1922

3 Allen, F. M. The Pathology of Diabetes, J Metabol Res 1 165-251 (Feb) 1922

4 Joslin, E. P. The Treatment of Diabetes Mellitus, Ed 3, Philadelphia, Lea & Febiger, 1923, p 137

logical explanation" The typical pathology of the disease was first noted by Opie⁵ in 1900, and later by Weichselbaum and Stangl,⁶ who described the hydropic degeneration and vacuolization of the island cells. In studying the pathology of the pancreas in diabetes in human beings, Allen found few specimens of the pancreas which did not show marks of some damage or infection as the presumable cause of diabetes. These changes, as a rule, involved a quantitative loss in the number of islands, due to hyalinization and fibrosis. The effect of acute infections on the pancreas has been noted by Mallory⁷ and consists chiefly in mitosis and regeneration of the cells in the islands, an indication of a preceding destruction or damage to these cells. In hemochromatosis or diabète bronzé we have a clear picture of pancreatic fibrosis and cellular degeneration, both insular and acinous, together with glycosuria.

In addition to the probability that pancreatic pathology is always an antecedent to the occurrence of diabetes mellitus, there exists further clinical and pathologic evidence that the primary or associated cause may be found in disease of the biliary tract. Moynihan⁸ says, "chronic pancreatitis is generally due to gallstone irritation." The importance of the early recognition and treatment of chronic pancreatitis cannot be exaggerated, for the disease, if left unchecked, may produce such sclerosis of the gland that the whole secretory substance and the islands of Langerhans may be destroyed. The result is diabetes." Judd⁹ believes that "cholecystitis is nearly always associated with a certain grade of hepatitis or pancreatitis, or both." Pancreatitis occurs frequently with cholecystitis and, as a result, a definite gross change occurs in the pancreas. It is possible for infection to invade the pancreas by way of the lymphatics from the gallbladder, and in many cases this probably explains the source of infection, it is apparently entirely relieved by treatment for cholecystitis." A comprehensive report by Lichty and Woods¹⁰ on the significance of glycosuria in gallbladder disease contributes further suggestive evidence in the same direction. That hepatitis is usually associated with gallbladder

5 Opie, E T Diabetes Mellitus Associated with Hyaline Degeneration of the Islands of Langerhans of the Pancreas, Bull Johns Hopkins Hosp **12** 263, 1901

6 Weichselbaum, A., and Stangl, E Zur Kenntnis der feineren Veränderungen des Pankreas bei Diabetes Mellitus, Wien klin Wchnschr **14** 968, 1901

7 Mallory, F B Quoted by Joslin, footnote 4

8 Moynihan, B Abdominal Operations, Ed 3, Philadelphia, W B Saunders Company, 1914, pp 402, 403

9 Judd, E S Relation of the Liver and the Pancreas to Infection of the Gallbladder, J A M A **77** 197 (July 16) 1921

10 Lichty, J A, and Woods, J O Significance of Glycosuria in Gallbladder and Duct Diseases, Am J M Sc **167** 1 (Jan 1) 1924

disease has been emphasized by Judd⁹ and Peterman et al,¹¹ and it is recognized that in catarrhal jaundice, a disease largely involving the liver, there may be an associated glycosuria. Of great interest in this connection is a very recent report by Frissell and Hajek.¹² These authors mention the development of glycosuria in three young girls following an attack of infectious jaundice. In two of the patients the glycosuria was apparently transient, but in the third case a full-blown and rather severe case of diabetes mellitus resulted.

That there is a close relationship between the liver and pancreas in carbohydrate metabolism is unquestioned. Various theories have been propounded attempting to explain the rôles played by these organs in the utilization of glucose, but until the isolation and use of insulin little concrete evidence had been obtained as to the actual processes concerned. A recent review of the subject by MacLeod¹³ indicates clearly two facts. In diabetic animals the administration of insulin enables the liver to store glycogen, and is associated with a rise in the respiratory quotient. The exact significance of the latter is not entirely clear, although it undoubtedly indicates an increased utilization of glucose. Although numerous investigators have made extensive studies of the subject, there is still a question as to the exact mechanism by which glucose is utilized. Whether the existing glucose is changed into an active form, the so-called gamma glucose of Winter and Smith,¹⁴ or whether the tissues are enabled to oxidize more readily glucose or the liver to supply it in an available form, is still unknown. According to Geelmuyden¹⁵ and other German investigators, insulin acts by inhibiting the overproduction, by the liver and other tissues, of glucose from fat, a distinctly novel theory. Whatever the precise mechanism involved may be, it is evident that in diabetes mellitus the diminution or absence of the internal secretion is the primary consideration, but it is also probable that in addition there is a marked disturbance in hepatic function, which is associated with lack of glycogen formation and storage. Pathologically, it is well recognized that diabetic livers are practically depleted of their glycogen deposits. In this connection the striking work of Mann and Magath¹⁶ is of extreme interest. These

11 Peterman, M. G., Priest, W. S., and Graham, E. A. The Association of Hepatitis with Experimental Cholecystitis and Its Bearing on the Pathogenesis of Cholecystitis in the Human, *Arch Surg* **2** 92 (Jan) 1921.

12 Frissell, L. F., and Hajek, Joseph. Insulin in the Severer Forms of Diabetes, with Report of Cases, *Arch Int Med* **33** 230 (Feb) 1924.

13 MacLeod, J. J. R. Insulin, *Physiol Rev* **4** 21 (Jan) 1924.

14 Winter, L. B., and Smith, W. Nature of Sugar in the Blood, *J Physiol* **57** 100 (Dec) 1922.

15 Geelmuyden, H. C. Metabolism in Diabetes, *Klin Wchnschr* **2** 1677 (Sept 3) 1923.

16 Mann, F. C., and Magath, T. B. Studies in the Physiology of the Liver, *Arch Int Med* **30** 73 (July), 171 (Aug) 1922, *ibid* **31** 797 (June) 1923.

investigators, in animal experiments, conclusively showed that the liver is of great importance in the normal control of carbohydrate metabolism, and that there exists an intimate relation between the liver and the pancreas in this process. In their animals hepatectomy produced death due to hypoglycemia, on account of the removal of the chief agent for storage and production of available glucose. The hyperglycemia following pancreatectomy was found to depend in a large measure on the presence of the liver, since removal of that organ after pancreatectomy caused an immediate drop to an abnormally low level in the previously high blood sugar.

In this connection the work of Ohler and Broun¹⁷ is of interest. These investigators, in work as yet unpublished, have attempted to produce evidence of a disturbance of liver function in diabetes mellitus. The recently introduced dye test for hepatic function, phenoltetrachlorphthalein test, was employed in studying a series of diabetic patients. In no case without obvious liver pathology was there any abnormal retention of the dye in the blood serum. Although such results undoubtedly indicate the absence of profound liver changes, it is to be questioned whether they present any evidence against the existence of a functional disturbance of the liver in diabetes mellitus. It is also of interest to mention the fact that these observers found that cases of liver disease of sufficient severity to show a retention of phenoltetrachlorphthalein in the blood stream also showed a reduced sugar tolerance. It may be added that present evidence would seem to indicate that the dye test for liver function, although an improvement on many older methods, still leaves much to be desired as a method for detecting any but gross disturbances of liver function.

That the internal secretion of the island cells of the pancreas and the integrity of the hepatic function are not the only factors affected in diabetes mellitus, and that insulin alone may not be entirely sufficient in controlling all the features of the disease, is suggested by recent investigative reports. Allen³ is responsible for the statement that the differences that still exist between a "total" diabetic animal and a totally pancreatectomized animal "furnish evidence, first, that the profound cachexia following total pancreatectomy is not due solely to the failure of carbohydrate metabolism or the hyperglycemia or glycosuria resulting from this failure, and second, that the alpha duct acinous or other cells of the pancreas furnish an unknown internal secretion, which is somehow important for the welfare of the organism." Somewhat similar conclusions have been reached by Fisher,¹⁸ who attempted

17 Ohler, W R, and Broun, G O Boston City Hospital, personal communication

18 Fisher, N F Attempts to Maintain Life of Totally Pancreatectomized Dogs Indefinitely by Insulin, Am J Physiol 67 634 (Feb) 1924

to keep alive pancreatectomized dogs by the use of insulin. Only those dogs in which there was some apparent regeneration of the duodenal stump of the pancreatic duct were observed to remain alive for long periods of time. He concludes that insulin probably does not represent the entire pancreas hormone complex, since in the total absence of the pancreas insulin cannot maintain life or does not control all the diabetic symptoms (subnormal weight, polyphagia, polyuria).

In view of the foregoing experimental and clinical data it is evident that diabetes mellitus, in addition to the known diminution of the internal secretion of the island cells of the pancreas, may well exhibit abnormalities in liver function and in the external secretory activity of the pancreas. It is with the hope of providing acceptable evidence of such a derangement of the normal physiologic processes that the following observations are presented. The studies consist in estimations of the pancreatic enzyme activity and the bile pigment concentration of the duodenal contents in sixty-eight cases of diabetes mellitus.

CLINICAL MATERIAL

The cases under consideration consist of an unselected group of sixty-eight cases of diabetes mellitus, taken from the wards of the Massachusetts General Hospital and the New England Deaconess Hospital. The youngest patient was aged 11 years, the oldest aged 72. The average age was 44 years. Of the sixty-eight patients, about 80 per cent were over 20, and nearly half of the patients were aged 50 or over. The age distribution in these cases is fairly representative of the disease, although there is probably a slight preponderance of cases in adult life. The distribution by sexes was essentially that accepted in most of the statistical data, i.e., females 55 per cent, males 45 per cent. The average known duration of the disease was about two and three-quarters years. In a few patients the disease had apparently existed for only one or two months, and in several cases symptoms had been present for well over ten years.

Although the majority of the patients entered the hospital for dietary regulation, twenty-eight of them were in a state of mild or severe acidosis on admission. Twelve patients were examined while definitely acidotic. One patient entered the hospital in a deep coma from which he recovered, following the administration of insulin. Thirteen exhibited, on admission, infection or gangrene. There were three cases of hemochromatosis, and one of cancer of the body and tail of the pancreas. One patient had a known history of acute pancreatitis requiring surgical intervention, a second one was known to have chronic pancreatitis following a long period of gallbladder attacks, and two others were probable cases of chronic pancreatitis. Thirty-one patients showed marked arteriosclerosis, a finding entirely consistent with the

age distribution of the cases. Regarding the incidence of gallbladder disease more will be said in the discussion of the laboratory findings.

The foregoing group of patients constitutes a fair average group of hospital diabetic patients, with the possible exception of the three cases of hemochromatosis. In spite of the number of patients showing more or less evidence of acidosis, the average severity of the group is but little higher than that of any similar number of patients with the disease.

In addition to the before mentioned patients, a group of ten normal persons was studied for normal control figures.

METHOD

The methods employed in the examination of these patients have been described in articles already published, and are, briefly, as follows. The patients were invariably examined in a state of fasting. A duodenal tube was passed into the duodenum and the position of the tip verified by fluoroscopic examination. As soon as the tip of the tube was in the middle of the second portion of the duodenum, 50 cc of a warm 33 per cent solution of magnesium sulphate was instilled into the duodenum. Shortly thereafter a free flow of bile was obtained, due to the relaxation of the sphincter of Oddi, and collection of the contents was made for the next half hour. At the end of this period the patient was given a test meal of 40 cc of 40 per cent cream by mouth. As soon as the cream was observed in the duodenal contents, a separate collection was made for a period lasting one hour.

The first portion of the duodenal contents was examined as soon as collected for bile pigments and sediment. The second portion, collected after the cream meal, was examined for pancreatic enzyme activity.

The method of examining the duodenal contents for bile pigments has been described in a recent article¹⁹ and is here quoted.

To 10 cc of duodenal contents add an equal amount of a saturated alcoholic solution of zinc acetate. This is shaken and filtered, and to 10 cc of the filtrate is added 1 cc of Ehrlich's reagent. This solution is allowed to stand in the dark for fifteen minutes and is then examined spectroscopically for the presence of bilirubin, urobilin, and urobilinogen. The number of dilutions with 95 per cent alcohol necessary to remove the characteristic absorption band of a given pigment is taken as the relative amount of that pigment in a given specimen. The absorption bands of urobilin and urobilinogen are absolutely characteristic. Although it has been said that bilirubin gives no characteristic shadow in the spectrum, I have found that pure solutions of this pigment give a distinctly characteristic shadow in the blue-violet end of the spectrum. As the concentration of this pigment increases, the shadow involves the blue-green, and even the yellow-green. In such instances the shadow includes the band made by the urobilin present and renders it impossible to estimate the latter pigment. In this event the original sample, after being treated with zinc acetate and Ehrlich's reagent, is split in two portions. One specimen is examined for the presence of bilirubin and urobilinogen, and

the dilutions estimated. The second fraction is treated with an equal amount of a 10 per cent solution of calcium chloride. The addition of the calcium precipitates sufficient bilirubin to permit the estimation of the urobilin present. In normal persons the normal concentrations have been found to be bilirubin, from 60 to 150 dilutions, urobilin, 4 to 16 dilutions, urobilinogen, from 0 to 4 dilutions.

At the time when this investigation was commenced attempts to estimate the urobilin content were unsatisfactory, and as a result some of the cases included in the tables have no figure for urobilin.

Estimation of the sediment was also performed by the method outlined in the above article. It consists in high speed centrifugalization of specimens of the duodenal contents for fifteen minutes, and subsequent microscopic examination of the sediment thus obtained. The observations made by Jones¹⁹ indicate clearly that the finding of abnormal amounts of cholesterol, bilirubin or calcium bilirubin crystals in the duodenal sediment constitutes strong evidence for a diagnosis of cholelithiasis. These observations were made on a large number of cases, and the conclusions seem to have been entirely justified by further clinical experiences. The findings of large amounts of bile-stained cells, epithelium or leukocytes has been found to be highly suggestive of biliary tract inflammation, but is not diagnostic of any given disease entity. Other microscopic findings are probably of no significance, and the examination of the sediments in this group of cases was entirely confined to a search for the above-named elements.

The method used for the determination of enzymatic activity was originally described by McClure, Wetmore and Reynolds,²⁰ and was subsequently employed by McClure and Jones²¹ in a clinical study of cases of pancreatic disease. By means of this method, the latter were able to demonstrate a marked diminution of proteolytic, lipolytic, or amylolytic activity below previously determined minimum normal limits in patients with known pancreatic pathology. The technic briefly described is as follows:

Proteolytic activity is estimated by allowing a dilution of the duodenal contents to act on a solution of soluble casein. The casein not affected by proteolytic action is precipitated by means of metaphosphoric acid solution. The index of proteolytic activity is taken as the number of milligrams of nitrogen not precipitated by the metaphosphoric acid. This nitrogen value is determined by an adaptation of the method of Folin and Wu for the determination of nonprotein nitrogen in the blood. Amylolytic activity is estimated

19 Jones, C. M. The Rational Use of Duodenal Drainage. An Attempt to Establish a Conservative Estimate of the Value of This Procedure in the Diagnosis of Biliary Tract Pathology, *Arch. Int. Med.* **34**: 60 (July) 1924.

20 McClure, C. W., Wetmore, A. S., and Reynolds, Lawrence. New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man, *Arch. Int. Med.* **27**: 706 (June) 1921.

21 McClure, C. W., and Jones, C. M. Studies in Pancreatic Function, *Boston M. & S. J.* **187**: 909 (Dec. 21) 1922.

as the number of milligrams of glucose developed by action of duodenal contents on a solution of soluble starch. The index of amylolytic activity is taken as the total number of milligrams of glucose developed, as determined by the method of Folin and Wu for the determination of sugar in the blood. Lipolytic activity is estimated by allowing duodenal contents to act on a true emulsion of cottonseed oil, and determining the amount of acidity developed by titrating with tenth normal alcoholic solution of sodium hydroxid. The number of cubic centimeters of tenth normal sodium hydroxid necessary to neutralize the acidity developed is used as the index of lipolytic activity. The samples of duodenal contents and the reagents used must be controlled for the presence of nitrogen not precipitated by metaphosphoric acid, for copper reducing bodies and for acidity.

The figures established by McClure and his associates as the minimal values for enzymatic activity were as follows: proteolytic, 2.0 mg nonprotein nitrogen, lipolytic, 1 cc of tenth normal sodium hydroxid, amylolytic, 1 mg glucose. As may be seen in Table 1, the

TABLE 1.—Comparison of Duodenal Findings in Normal Controls and Diabetic Patients

	Pancreatic Enzyme Activity			Duodenal Bile Pigments			Sediment
	Proteo- lytic, Mg Non protein Nitrogen	Lipo- lytic, Cc N/10 Sodium Hydroxid	Amylo- lytic, Mg Glucose	Urobil- ogen Dilution Units	Uro- bilin Dilution Units	Bili- rubin Dilution Units	
Standard values	1.5	0.75	0.75	4	16	150	0
Average findings in 10 normal persons	2.8	1.6	2.2	0	12	120	0
Average findings in 68 diabetic patients	1.9	1.0	2.5 (57 cases)	10	25 (41 cases)	240	11
Average findings in cases showing abnormalities	1.06	0.40	0.40	24	44	313	—
Per cent abnormalities in 68 diabetic patients	33%	37%	9%	40%	50%	67%	19%

average results obtained in studying our group of normal controls were all well above McClure's minimal values. On rare occasions, however, we have obtained in normal persons, isolated figures slightly below these values. In order to obtain results that will leave little room for criticism we have arbitrarily chosen for minimal values figures which are but 75 per cent of McClure's lowest normal figures. Thus, we have assumed that values below the following may be safely construed as showing evidence of diminished pancreatic enzymatic activity: proteolytic, 1.5 mg nonprotein nitrogen, lipolytic, 0.75 cc tenth normal sodium hydroxid, amylolytic, 0.75 mg glucose.

INVESTIGATIVE FINDINGS

Examination of Table 1 reveals several facts of interest. The average findings in the determination both for activity and bile pigment elimination in the group of normal controls were all well within normal limits.

The enzyme estimations were far above even the minimal values given by McClure, and the bile pigment estimations were below the upper limits of normal. An average of the various findings on the group of sixty-eight diabetic patients shows that the estimation for proteolytic and lipolytic activity was distinctly below the average figures for the normal controls, but were above our minimal normal limits. Figures for amylolytic activity were above the normal control averages, and very much higher than our minimal values. The average values for the individual bile pigments, however, were all far in excess of control figures, and the normal standard limits.

In spite of the fact that the average figures for enzymatic activity in diabetic patients do not show a diminution below our arbitrarily adopted minimal standards, it is to be noted that the protein and fat splitting enzyme average values were just at the lower levels established by McClure. Turning from average figures to individual results, however, we find that 33 per cent of the cases showed proteolytic activity below our figure of 1.5 mg nonprotein nitrogen, and 37 per cent were below our minimum figure of 0.75 cc tenth normal sodium hydroxid for lipolytic activity. In the case of the starch-splitting enzyme, only 9 per cent of the cases developed values below 0.75 mg glucose.

From the bile pigment estimations it was found that 40 per cent of the cases showed abnormally high values of urobilinogen, 56 per cent for urobilin, and 67 per cent gave high values for bilirubin.

Of the entire sixty-eight cases, thirty-three, or 49 per cent showed a diminution in the activity of one or more enzymes, and fifty-one cases, or 76 per cent, showed an abnormal output of one or more of the bile pigments. Twenty-three cases, or one-third of the total number studied, showed abnormalities both in the enzymatic activity and bile pigment elimination.

Examination of the last line of data in Table 1 reveals the average level of enzyme and bile pigment estimations in those cases showing any abnormality. The general average of this group of cases is not only different from that of the normal controls, but is strikingly abnormal in relation to our minimal enzyme and maximum pigment limits.

Studies of the duodenal sediments showed eleven cases, or 19 per cent, in which there was a large amount of cholesterol or bile pigment crystals. Four more cases showed large amounts of bile-stained cells, both epithelial and leukocytic.

In order to attempt an analysis of the significance of the foregoing findings a tabulation has been made of the usual variables in diabetic patients, and the percentage of abnormal findings under these varying

conditions has been outlined. Table 2 indicates the effect of the most common variables in diabetes mellitus, namely, sex, age, duration of the disease, the fasting blood-sugar level at the time of examination, the diet in calories per kilogram of body weight, and the administration of insulin, both as regards dosage and duration of treatment.

TABLE 2—*Effect of Change in Usual Diabetic Variables*

Diabetic Variables	Number Cases	Percentage of Cases with Abnormal Enzyme Activity	Percentage of Cases with Abnormal Bile Pigments
Average findings on 68 diabetic patients	68	49	76
Sex			
Male	31	47	80
Female	37	57	73
Age			
Under 30 years	13	69	69
30 to 50 years	21	43	72
Over 50 years	34	55	85
Duration of Diabetes			
Under 1 year	20	53	84
1 to 3 years	22	41	68
Over 3 years	26	65	73
Fasting Blood Sugar			
Under 0.15 per cent	27	42	80
0.15 to 0.20 per cent	16	56	56
Over 0.20 per cent	22	59	86
Diet, Calories per Kg. of Body Weight			
Under 10 calories	8	50	100
10 to 20 calories	26	56	80
20 to 30 calories	18	33	72
Over 30 calories	15	66	66
Insulin Therapy			
No insulin	38	49	73
Under 10 units per day	10	30	80
10 to 20 units per day	11	55	90
Over 20 units per day	9	89	66
Insulin Therapy			
No insulin	38	49	73
4 days or under	13	30	70
Over 4 days	17	53	76

TABLE 3—*Effect of Complications on Diabetes*

Complications	Number Cases	Pancreatic Enzyme Activity, per Cent Abnormal	Duodenal Bile Pigments, per Cent Abnormal
Average determinations on 68 cases	68	49	76
Acidosis within 2 weeks	15	41	94
Acidosis at examination	12	50	75
Sepsis, gangrene	10	50	90
Marked arteriosclerosis	31	50	77
Gallbladder disease (probable)	15	53	60
Pancreatitis (probable)	4	100	100
Hemochromatosis	3	100	0

In Table 3 we have attempted to outline the effect of complicating factors on the pancreatic and hepatic activity. Acidosis, sepsis, gangrene, arteriosclerosis, gallbladder disease, pancreatitis, and hemochromatosis are tabulated in order named, with the apparent relation of each factor to the percentage of abnormal findings.

Table 4 gives in detail the average findings in five cases which were examined more than once. In each case the initial examination was made while the patient was in a state of severe acidosis. A second observation was made at a subsequent date when the patient had apparently recovered from the acidosis. From the values in this table, it is obvious that in these patients recovery from acidosis was associated with a marked change in pancreatic and hepatic function.

In Table 5 all of the important data on each individual diabetic patient are given in full detail. The findings include sex, age, duration of the disease, urinary and blood sugar at the time of examination, the presence or absence of urinary diacetic acid, weight in kilograms, dietary intake in calories per kilogram of body weight, insulin dosage, the enzymatic and bile pigment estimations, sediment findings, and any other data of importance. Examination of this table shows that, in

TABLE 4—Changes Occurring After Recovery from Severe Acidosis

	Pancreatic Enzyme Activity			Duodenal Bile Pigments		
	Proteolytic	Lipolytic	Amylolytic	Urobilinogen	Urobilin	Bilirubin
Standard values	1.5	0.75	0.75	4	16	150
Average findings in 5 patients during acidosis	1.36	0.61	2.61	16	46	281
Average findings in same 5 patients after recovery	1.88	1.12	1.98	1.2	26	202
Percentage apparent improvement in function	+28%	+89%	-24%	+920%	+43%	+25%

spite of the average level of enzymatic activity being above the minimum normal figures, a large number of cases showed striking reductions in enzyme action. In six cases (Cases 9, 17, 23, 34, 39, 41) one or more of the enzymes showed almost negligible findings, and in one case (Case 56) it was impossible to produce any evidence of enzymatic activity. In the last named case, identical findings were obtained at a subsequent examination one year later. It is obvious from Table 1 that those cases showing abnormal findings gave average values of from 30 to 45 per cent below our minimal normal figures, and over 50 per cent below McClure's minimum values. Similarly, in the bile pigment estimations, those cases showing abnormalities gave average findings of 150 per cent or more above the upper limits of normal. In the face of such findings, therefore, there can be little doubt that real abnormalities exist both in pancreatic enzyme activity and in bile pigment metabolism in a large percentage of cases of diabetes mellitus. These abnormalities consist in a diminution of the external secretory activity of the pancreas, and in an increase in the bile pigment metabolism.

TABLE 5—Summary of Data on Cases at Time of Intubation

Case No.*	Age	Sex	Duration in Years	Fasting Blood Sugar, per Cent	Urinary Sugar, per Cent	Diacetone Acid	Calories per Kg. Weight	Insulin per Day	Duodenal Findings			Bile Pigments			Remarks	
									Enzymatic Activity			Sediment				
									Proteo-type, Ms.	Lipo-type, Non protein Hydrogen C N/10	Amylolytic, Mg.	Urobilinogen, Dilution	Bilirubin, Dilution	Urobilin, Dilution		
1	14	M	1.0	0.16	0	0	38	32	1.4	1.4	3.6	0	4	64	Entered with icterus Cholelithiasis (?)	
2	17	M	1.5	0.24	0	0	86	56	4.0	1.9	6.8	6	24	370	+	
3	15	M	0.1	0.10	0	0	34	40	30	1.1	1.1	0	8	162	Entered with icterus Cholelithiasis (?)	
4	48	M	3.0	0.13	0	0	85	12	0	0.6	0.45	1.2	0	4	48	+
5	27	M	0.5	0.11	0	+	68	20	45	0.7	0.3	0.2	6	22	130	Entered with icterus, acute pancreatitis (?)
6	58	M	2.0	0.04	0	0	56	28	0	1.7	0.9	3.1	64	140	820	G ingrene, entered with icterus
7	50	F	7.0	0.16	0	0	47	33	30	2.5	1.7	2.3	3	16	266	Entered with icterus, sepsis
8	63	F	2.0	0.18	+	0	87	15	0	1.6	2.6	4	8	180	Entered with icterus, sepsis	
9	11	F	1.0	0.15	0.9	0	22	43	60	0.9	0.2	1.5	0	6	36	Entered with icterus, sepsis
10	51	F	0.6	0.17	0	0	60	25	7	2.7	1.8	3.6	0	12	130	Syphilitic
11	30	F	4.0	0.20	0	0	50	17	20	1.4	0.5	2.5	2	40	216	Entered with icterus, sepsis three weeks before
12	17	F	0.21	0.21	0.8	+	40	5	0	2.3	1.6	2.9	0	72	324	Entered with icterus, sepsis three weeks before
13	44	F	3.0	0.13	0.29	0	53	15	16	1.8	1.1	2.5	35	150	342	Entered with icterus, sepsis
14	53	F	3.1	0.17	0.20	0	60	11	6	3.0	1.1	0.5	4	108	216	Entered with icterus, sepsis
15	95	F	0.6	0.22	0	+	63	22	14	1.1	0.7	1.2	3	45	260	+
16	61	F	1.3	0.15	0	0	54	15	0	1.5	1.0	2.2	2	16	620	Entered with icterus, sepsis
17	58	F	2.0	0.17	0	0	85	24	0	+	0.05	0.2	0	6	57	+
18	56	F	2.0	0.28	+	0	60	12	6	2.1	1.3	3.3	4	22	288	Entered with icterus, sepsis
19	34	F	0.6	0.22	0	0	66	15	15	2.8	1.3	3.1	0	7	76	Entered with icterus, sepsis
20	23	F	1.0	0.38	0.3	0	53	12	0	2.6	0.9	3.2	0	18	132	Entered with icterus, sepsis
21	72	F	9.0	0.13	0	0	75	19	0	1.6	0.8	3.6	0	16	104	Entered with icterus, sepsis
22	45	F	0.28	0	0	0	80	87	9	2.8	1.3	4.6	12	28	216	Entered with icterus, sepsis
23	59	F	1.0	0.18	1.8	0	33	40	15	1.5	0.1	3.0	12	36	162	Entered with icterus, sepsis
24	38	F	8.0	0.14	0	0	80	14	0	1.2	0.5	1.4	6	37	270	Gangrene
25	55	F	0.3	0.26	1.8	+	82	12	6	3.0	1.6	4.6	0	33	258	Entered with icterus, sepsis
26	45	F	1.7	0.08	0	0	53	30	0	2.6	1.4	2.9	0	16	258	Entered with icterus, sepsis
27	49	F	0.1	0.08	0	0	84	21	0	1.8	1.6	2.6	0	12	259	Entered with icterus, sepsis
28	65	F	7.0	0.20	2.0	+	56	14	15	0.7	2.6	0	0	18	350	Entered with icterus, sepsis

29	62	130	0.15	6	0	45	31	8	15	26	11	35	21	2	6	144	0
30	62	180	0.21	0.2	0	49	14	6	15	24	10	34	27	2	10	241	0
31	57	80	1.0	0.25	0	0	55	23	38	42	19	0.4	30	2	0	321	+
32	50	50	0.5	0.09	0.23	0.2	64	69	22	15	21	0.2	34	0	0	321	+
33	33	39	0.5	0.09	0.23	0.2	60	18	27	27	18	0.7	31	0	0	300	0
34	34	56	0.5	0.09	0.23	0.2	60	60	23	13	11	1.1	35	10	162	0	0
35	36	61	0.6	0.11	0.2	0.2	68	68	24	20	11	1.1	40	6	214	0	0
36	37	56	0.9	0.22	0.5	0.5	79	79	4	12	12	0.01	38	16	72	0	0
37	38	46	0.11	0.01	0.2	0.2	79	36	49	22	19	0.6	28	0	163	+	0
38	39	51	0.5	0.30	0.80	0.4	40	15	115	115	115	0.01	14	0	90	0	0
39	40	40	1.6	0.35	0.4	0.4	42	46	100	100	100	0.01	19	0	115	0	0
40	41	43	2.7	0.15	0.01	0.01	61	37	25	10	10	1.6	23	1	140	0	0
41	42	43	2.5	0.25	0.15	0.15	51	25	7	10	10	1.5	15	1	260	0	0
42	43	44	4.4	0.45	0.34	0.3	63	63	36	44	15	1.9	15	0	500	0	0
43	44	45	4.6	0.45	0.34	0.3	49	49	13	0.3	0.3	0.01	15	0	210	0	0
44	45	46	4.7	0.45	0.34	0.3	47	47	0	0	0	0.01	15	0	115	0	0
45	46	47	4.8	0.45	0.34	0.3	48	48	0	0	0	0.01	15	0	260	0	0
46	47	48	4.8	0.45	0.34	0.3	49	49	0	0	0	0.01	15	0	115	0	0
47	48	49	4.9	0.45	0.34	0.3	50	50	0	0	0	0.01	15	0	260	0	0
48	49	50	5.0	0.45	0.34	0.3	51	51	0	0	0	0.01	15	0	115	0	0
49	50	51	5.0	0.45	0.34	0.3	52	52	0	0	0	0.01	15	0	260	0	0
50	51	52	5.0	0.45	0.34	0.3	53	53	0	0	0	0.01	15	0	260	0	0
51	52	53	5.0	0.45	0.34	0.3	54	54	0	0	0	0.01	15	0	260	0	0
52	53	54	5.0	0.45	0.34	0.3	55	55	0	0	0	0.01	15	0	260	0	0
53	54	55	5.0	0.45	0.34	0.3	56	56	0	0	0	0.01	15	0	260	0	0
54	55	56	5.0	0.45	0.34	0.3	57	57	0	0	0	0.01	15	0	260	0	0
55	56	57	5.0	0.45	0.34	0.3	58	58	0	0	0	0.01	15	0	260	0	0
56	57	58	5.0	0.45	0.34	0.3	59	59	0	0	0	0.01	15	0	260	0	0
57	58	59	5.0	0.45	0.34	0.3	60	60	0	0	0	0.01	15	0	260	0	0
58	59	60	5.0	0.45	0.34	0.3	61	61	0	0	0	0.01	15	0	260	0	0
59	60	61	5.0	0.45	0.34	0.3	62	62	0	0	0	0.01	15	0	260	0	0
60	61	62	5.0	0.45	0.34	0.3	63	63	0	0	0	0.01	15	0	260	0	0
61	62	63	5.0	0.45	0.34	0.3	64	64	0	0	0	0.01	15	0	260	0	0
62	63	64	5.0	0.45	0.34	0.3	65	65	0	0	0	0.01	15	0	260	0	0
63	64	65	5.0	0.45	0.34	0.3	66	66	0	0	0	0.01	15	0	260	0	0
64	65	66	5.0	0.45	0.34	0.3	67	67	0	0	0	0.01	15	0	260	0	0
65	66	67	5.0	0.45	0.34	0.3	68	68	0	0	0	0.01	15	0	260	0	0
66	67	68	5.0	0.45	0.34	0.3	69	69	0	0	0	0.01	15	0	260	0	0
67	68	69	5.0	0.45	0.34	0.3	70	70	0	0	0	0.01	15	0	260	0	0
68	69	70	5.0	0.45	0.34	0.3	71	71	0	0	0	0.01	15	0	260	0	0
69	70	71	5.0	0.45	0.34	0.3	72	72	0	0	0	0.01	15	0	260	0	0
70	71	72	5.0	0.45	0.34	0.3	73	73	0	0	0	0.01	15	0	260	0	0
71	72	73	5.0	0.45	0.34	0.3	74	74	0	0	0	0.01	15	0	260	0	0
72	73	74	5.0	0.45	0.34	0.3	75	75	0	0	0	0.01	15	0	260	0	0
73	74	75	5.0	0.45	0.34	0.3	76	76	0	0	0	0.01	15	0	260	0	0
74	75	76	5.0	0.45	0.34	0.3	77	77	0	0	0	0.01	15	0	260	0	0
75	76	77	5.0	0.45	0.34	0.3	78	78	0	0	0	0.01	15	0	260	0	0
76	77	78	5.0	0.45	0.34	0.3	79	79	0	0	0	0.01	15	0	260	0	0
77	78	79	5.0	0.45	0.34	0.3	80	80	0	0	0	0.01	15	0	260	0	0
78	79	80	5.0	0.45	0.34	0.3	81	81	0	0	0	0.01	15	0	260	0	0
79	80	81	5.0	0.45	0.34	0.3	82	82	0	0	0	0.01	15	0	260	0	0
80	81	82	5.0	0.45	0.34	0.3	83	83	0	0	0	0.01	15	0	260	0	0
81	82	83	5.0	0.45	0.34	0.3	84	84	0	0	0	0.01	15	0	260	0	0
82	83	84	5.0	0.45	0.34	0.3	85	85	0	0	0	0.01	15	0	260	0	0
83	84	85	5.0	0.45	0.34	0.3	86	86	0	0	0	0.01	15	0	260	0	0
84	85	86	5.0	0.45	0.34	0.3	87	87	0	0	0	0.01	15	0	260	0	0
85	86	87	5.0	0.45	0.34	0.3	88	88	0	0	0	0.01	15	0	260	0	0
86	87	88	5.0	0.45	0.34	0.3	89	89	0	0	0	0.01	15	0	260	0	0
87	88	89	5.0	0.45	0.34	0.3	90	90	0	0	0	0.01	15	0	260	0	0
88	89	90	5.0	0.45	0.34	0.3	91	91	0	0	0	0.01	15	0	260	0	0
89	90	91	5.0	0.45	0.34	0.3	92	92	0	0	0	0.01	15	0	260	0	0
90	91	92	5.0	0.45	0.34	0.3	93	93	0	0	0	0.01	15	0	260	0	0
91	92	93	5.0	0.45	0.34	0.3	94	94	0	0	0	0.01	15	0	260	0	0
92	93	94	5.0	0.45	0.34	0.3	95	95	0	0	0	0.01	15	0	260	0	0
93	94	95	5.0	0.45	0.34	0.3	96	96	0	0	0	0.01	15	0	260	0	0
94	95	96	5.0	0.45	0.34	0.3	97	97	0	0	0	0.01	15	0	260	0	0
95	96	97	5.0	0.45	0.34	0.3	98	98	0	0	0	0.01	15	0	260	0	0
96	97	98	5.0	0.45	0.34	0.3	99	99	0	0	0	0.01	15	0	260	0	0
97	98	99	5.0	0.45	0.34	0.3	100	100	0	0	0	0.01	15	0	260	0	0
98	99	100	5.0	0.45	0.34	0.3	101	101	0	0	0	0.01	15	0	260	0	0
99	100	101	5.0	0.45	0.34	0.3	102	102	0	0	0	0.01	15	0	260	0	0
100	101	102	5.0	0.45	0.34	0.3	103	103	0	0	0	0.01	15	0	260	0	0
101	102	103	5.0	0.45	0.34	0.3	104	104	0	0	0	0.01	15	0	260	0	0
102	103	104	5.0	0.45	0.34	0.3	105	105	0	0	0	0.01	15	0	260	0	0
103	104	105	5.0	0.45	0.34	0.3	106	106	0	0	0	0.01	15	0	260	0	0
104	105	106	5.0	0.45	0.34	0.3	107	107	0	0	0	0.01	15	0	260	0	0
105	106	107	5.0	0.45	0.34	0.3	108	108	0	0	0	0.01	15	0	260	0	0
106	107	108	5.0	0.45	0.34	0.3	109	109	0	0	0	0.01	15	0	260	0	0
107	108	109	5.0	0.45	0.34	0.3	110	110	0	0	0	0.01	15	0	260	0	0
108	109	110	5.0	0.45	0.34	0.3	111	111	0	0	0	0.01	15	0	260	0	0
109	110	111	5.0	0.45	0.34	0.3	112	112	0	0	0	0.01	15	0	260	0	0
110	111	112	5.0	0.45	0.34	0.3	113	113	0	0	0	0.01	15	0	260	0	0
111	112	113	5.0	0.45	0.34	0.3	114	114	0	0	0	0.01	15	0	260	0	0
112	113	114	5.0	0.45	0.34	0.3	115	115	0	0	0	0.01	15	0	260	0	0
113	114	115	5.0	0.45	0.34	0.3	116	116	0	0	0	0.01	15	0	260	0	0
114	115	116	5.0	0.45	0.34	0.3	117	117	0	0	0	0.01	15	0	260	0	0
115	116	117	5.0	0.45	0.34	0.3	118	118	0	0	0	0.01	15	0	260	0	0
116	117	118	5.0	0.45	0.34	0.3	119	119	0	0	0	0.01	15	0	260	0	0
117	118	119	5.0	0.45	0.34	0.3	120	120	0	0	0	0.01	15	0	260	0	0
118	119	120	5.0	0.45	0.34	0.3	121	121</td									

COMMENT

In view of the before mentioned findings it is of interest to discuss the probable significance of these alterations in pancreatic and hepatic function, and to comment briefly on the various factors concerned in their production. The first fact of importance is the diminution in the enzymatic activity of the duodenal contents. As already noted, nearly one-half of the cases showed a diminution in the activity of one or more of the pancreatic enzymes. The striking fact in these findings is that amylolytic activity was apparently diminished in only 9 per cent of the cases, whereas proteolytic activity and lipolytic activity showed definite reductions below the minimum normal level in over a third of the cases. Just why there should be a dissociation of these ferment actions is extremely interesting, and at present we can offer no reasonable explanation of this fact. The changes described, however, can apparently have but one significance, namely, that the duct or acinous cells of the pancreas are severely damaged in a large proportion of cases of diabetes mellitus. Such a disturbance may be purely functional, or, as is more likely, may be anatomic.

To what extent the reduction in pancreatic enzyme activity noted in our cases may influence the symptomatology and course of the disease it is difficult to surmise. It is certain that in most cases the effect of this diminution of digestive activity can be at least partially compensated for by the presence of other ferments in the digestive tract. It is also certain that even striking abnormalities in the external secretion of the pancreas may be present without marked symptomatology, and not infrequently cases of cancer of the pancreas, in which the major part of the gland is entirely replaced by neoplastic tissue, are encountered without other symptoms than an unexplained weakness and some loss of weight. The observations of Allen and Fisher, referred to in the foregoing, would seem to indicate, however, that in pancreatectomized animals an additional factor to the loss of the internal secretion of the organ may contribute definitely to the symptoms of the disease. In Fisher's experiments the loss of weight, polyphagia and polyuria were inadequately relieved by insulin therapy alone and the animals did not survive. It may well be, therefore, that a marked diminution in proteolytic and lipolytic activity in cases of diabetes mellitus may contribute definitely to the symptomatology of the disease. Such symptoms, are, however, of relatively minor importance in the majority of cases, and are at present impossible to define. It is also improbable that in most cases the degree of disturbance of the external secretory activity of the pancreas, exhibited in our findings, exerts a very definite influence on the prognosis of the disease except where the actual degree of pancreatic damage is extreme. In

cases of chronic pancreatitis following acute pancreatitis, the usual resulting diabetes is generally severe and of short duration. Hemochromatosis, a disease in which the damage to the pancreatic tissue is widespread, is also usually marked by severe diabetes. With the exception of such cases, however, it would seem that disturbances of the external secretion of the pancreas exert little evident effect on the duration or severity of the disease. A practical point, however, may be noted here regarding the results of long continued diminution in the digestive activity of the pancreatic secretion. If such diminution is of sufficient degree there very well may be an associated disturbance in the actual absorption of food products. Diminished proteolytic and lipolytic activity might well be reflected in a diminished absorption of protein and fat, with a resulting increase in the protein and fat content of the stools. Such a theoretical consideration may possibly help to explain the apparent inability of certain diabetic patients to progress satisfactorily on a given diet, owing to the fact that a certain proportion of the food intake is lost in the stools. A further consideration is suggested by the fact that the largest percentage of abnormalities was noted in the determinations of lipolytic activity. Inability to split fat properly may explain the intestinal symptoms that are not too infrequently met with in patients with severe diabetes. Intermittent diarrhea is not uncommon in severe cases and during these attacks free fat and fatty acids appear in the stools in abnormal amounts. Although such intestinal disturbances are usually attributed to asthenia, plus an irritating diet of fruit or coarse vegetables, it is an interesting assumption to consider such phenomena as primarily due to an inability to split and absorb fat completely. Case 20 is a case in point. This patient was a woman, aged 59, with rather severe diabetes of one year's duration. Diarrhea was an outstanding symptom, and it is to be noted that the activity of the pancreatic lipase was reduced to almost a negligible quantity.

It is evident from a close examination of Table 5 that the severity of the diabetes does not necessarily run parallel to the degree of disturbance of the external pancreatic secretion. A striking example of this is seen in Case 41 from the New England Deaconess Hospital. This patient, a woman, aged 46, was first diagnosed as a diabetic patient about eleven years before the present examination. During those years she had been seen repeatedly by competent physicians, and had repeatedly shown hyperglycemia and glycosuria. At the time of our examination she was very much emaciated and weighed only 35 kg (78 pounds). She was consuming a diet that afforded her 52 calories per kilogram of body weight, was sugar free, and had a normal blood sugar, without the use of insulin. In spite of this remarkable food intake she showed

no demonstrable proteolytic activity, and only a small amount of lipolytic activity Amylolytic activity was within normal limits With some few exceptions, of which the foregoing is an interesting example, those that were clinically mild diabetic patients tended to show little or no reduction in the enzymatic activity of the pancreas The question naturally arises in a discussion of the cause of the reduction in enzyme activity, whether such a reduction may not be due primarily to emaciation alone It is well known that marked undernutrition, with the resulting loss of weight, is accompanied by changes in the size and function of the pancreas Loss of more than 30 per cent of the body weight is said to be associated with demonstrable loss in pancreatic function In such patients as Case 46, before mentioned, it is entirely possible that undernutrition played a part in the reduction of pancreatic enzyme activity The majority of the patients included in this series, however, were not extremely emaciated, and the lowest figures for enzyme activity were not necessarily found in patients who were strikingly under weight We have frequently found high values for enzyme activity in patients who were very emaciated, both in this series, and in examinations made on patients suffering from other diseases It can be said, therefore, that undernutrition is an important factor in the reduction of pancreatic function, but it is certainly not the only one Olmsted²² has recently obtained observations, by using methods identical with ours, that point out clearly the importance of undernutrition in reducing pancreatic activity

The significance of alterations in the bile pigments of the duodenal contents has been fully discussed in earlier communications²³ Briefly it may be said that increased amounts of bilirubin, urobilin or urobilinogen in the bile excreted into the duodenum are abnormal, and indicate one of two things, increased blood destruction or abnormal liver function In cases of diabetes the first factor obviously may be disregarded Any marked increase in the elimination of one or several of the before mentioned pigments may probably be taken, therefore, as evidence of disturbed liver function It has already been indicated that we do not know the exact nature of the disturbance of liver function that may exist in this disease It may logically be assumed, however, that any alterations noted in bile pigment elimination in diabetes mellitus may properly be interpreted as an indication of an alteration in total metabolic activity of the hepatic parenchyma This

22 Olmsted, W H Department of Internal Medicine, Washington University, St Louis, personal communication

23 Jones, C M Blood Pigment Metabolism and Its Relation to Liver Function, Arch Int Med 29 643 (May) 1922, Jones, C M, and Minot, G R Infectious (Catarrhal) Jaundice An Attempt to Establish a Clinical Entity, Boston M & S J 189 531 (Oct 18) 1923

metabolic change is most likely a change associated with glycogen production, storage and mobilization, and any change in pigment metabolism is simply a reflection of alterations in the general liver processes. Examination of Table 1 shows that 67 per cent of the patients showed increased elimination of bilirubin, 56 per cent showed abnormal amounts of urobilin, and 40 per cent were putting out excessive amounts of urobilinogen. The order of frequency in which the abnormalities were noted in the three pigments is entirely in keeping with previous results. We have found, in studying other types of cases, that those with alteration in hepatic function most frequently present abnormalities in bilirubin elimination, next in that of urobilin, and lastly in urobilinogen. Seventy-six per cent of the cases in this series showed abnormally high values for one or more of the pigments. Such a high percentage of abnormal values for bile pigment elimination would seem to be clear evidence of an abnormal liver function or activity in diabetes mellitus. Whatever the exact nature of this disturbance of hepatic function may be, it appears likely that there is an abnormal, undesirable and probably inefficient type of work done by the liver in this disease.

That there is an intimate relation between the abnormalities in pancreatic and liver function already noted would seem indicated by the fact that in one-third of the cases there were marked changes in both enzyme and bile pigment estimations.

An attempt has been made in Tables 2, 3 and 4 to analyze some of the alterations noted in enzyme or pigment estimations. Obviously it is impossible to determine precisely the effect of any given variable, but the general trend of the influence of various factors may perhaps be indicated. In Table 2 the usual diabetic variables have been considered. Variations in sex, age, duration of the disease, and the fasting blood sugar on the day of examination seemed to exhibit no characteristic changes from the general percentages, either in pancreatic enzyme activity or bile pigment elimination. In considering the effect of diet, however, it is evident that those cases having a very low caloric intake per kilogram of body weight showed the most frequent occurrence of abnormal bile pigment elimination. Conversely, those patients on the highest caloric intake showed the fewest abnormalities. It is also of interest to note that all of those patients who were on an intake of less than 10 calories per kilogram of body weight showed abnormal pigment values, and these pigment abnormalities were among the most marked of any in the series. It seems logical to assume, therefore, that starvation or existence on a very low caloric diet is associated with a marked increase in liver activity. This increase may be due to the mobilization of available fat and glycogen. Such a process invariably

takes place during inanition, and is associated with an actual loss of liver substance

From an analysis of our figures it is difficult to determine the influence of insulin therapy on liver and enzyme activity. It would appear, however, that, when a sufficient quantity of insulin is given over a long enough period of time, there may be a reduction in the number of cases showing abnormalities in enzyme activity, bile and pigment metabolism. This may be due to an actual increase in food intake, or to a general improvement in tissue function following the use of insulin.

Table 3 represents an attempt to analyze the effect of certain complicating factors on hepatic and enzyme activity. Recent or existing acidosis, sepsis, gangrene, and the presence of marked arteriosclerosis seemed to have little or no special effect on the general percentage of abnormalities in the external pancreatic secretion. The presence of cholelithiasis, also, apparently exerted no characteristic influence on abnormal findings of enzyme activity, but all of the cases of probable pancreatitis showed marked reduction in digestive action of the duodenal contents. The cases of hemochromatosis all showed a similar change. Such findings are not surprising, on the contrary, it was to be expected that diseases directly associated with pathologic changes in the pancreas or biliary tract should exhibit such abnormalities.

An explanation of the bile pigment findings shown in Table 3 is somewhat difficult. Apparently, during an existing acidosis there is less change in liver activity than in the period immediately following. Sepsis has usually been associated with increased bile pigment elimination, and it was to be expected that cases with infection or general gangrene should show some increase in pigment estimations. The percentage of cases of cholelithiasis showing pigment abnormalities was the same as that of the entire group. The two rather striking exceptions to the average are the cases of pancreatitis and those of hemochromatosis. The results in the first group are not particularly surprising on account of the intimate relation between the pancreas and biliary tract. The absence of abnormal bile pigment values in the three cases of hemochromatosis was a distinct surprise, and, with our present lack of knowledge, suggests no ready explanation. An interesting conjecture is indicated, however, by the known pathology of this rare disease. Heavy pigment deposits always occur in the liver in hemochromatosis, and such deposits are largely composed of hemosiderin. Hemofuscin is also deposited in large amounts in the connective tissues. It is entirely possible that the lack of an increase in bile pigment elimination in this disease is due to the fact that any excess pigment, metabolized in the liver or elsewhere in the body, is retained in these pigment deposits.

A detailed theoretical discussion has been made of the various data outlined in Tables 2 and 3. We realize that the number of variable factors in any given case of diabetes render hypotheses based on findings in such small groups of cases extremely difficult of proof. Our intention has been only to indicate certain tendencies which appear to exist in relation to different factors in the disease. We realize that any accurate interpretation of the figures in these two tables is, of necessity, impossible.

Table 4 is of interest with regard to the probable effect of acidosis on the general body functions. Examination of the table indicates clearly that in these five cases there was a very striking improvement, both in enzymatic activity and liver function, following recovery from acidosis. With the single exception of the amylolytic activity, all the determinations showed a marked change in the direction of normalcy. Failure of this single enzyme to vary with the other two has been apparent throughout the study, and we are unable to assign any explanation to the behavior of this particular function of the pancreas. It will be noted that urobilinogen, which was the last to show abnormal changes in the presence of liver disturbance (Table 1), was the first pigment to return to normal, during the period of recovery from acidosis. Such a finding would seem to indicate that the presence of increased amounts of urobilinogen in the bile offers the surest evidence of liver disturbance that may be obtained by a study of the bile pigments, although increases in urobilin and bilirubin are undoubtedly of similar significance.

From the changes outlined in Table 4, one is forced to conclude that in severe acidosis there is a serious functional change in the liver and pancreas, as well as in other tissues of the body. In the case of the external secretion of the pancreas and the bile, the shift from very abnormal figures to normal during the recovery from acidosis is almost as striking as the well known changes that occur in the blood. That even mild acidosis is a serious condition for tissue function is almost universally accepted, but the truth of the statement is rendered all the more evident from findings similar to the above.

CONCLUSION

In closing, it is important that we consider briefly the relation of gallbladder disease to diabetes. In a previous paper,¹⁰ satisfactory evidence has been presented of the value of duodenal analysis in the diagnosis of gallstones. Abnormal amounts of cholesterol or bile pigment crystals in the duodenal sediment were shown to be present in the vast majority of cases of cholelithiasis, and only rarely in other diseases. As an aid in the diagnosis of gallstones, we have found such

evidence extremely satisfactory. Examination of Table 5 shows that eleven patients, or 19 per cent of the series, showed the characteristic findings of cholelithiasis, as judged by the foregoing criteria. In addition, two other patients (Cases 30 and 53) gave a history of previous operation for cholelithiasis, with the finding of stones at exploration. A third patient (Case 55) gave an absolutely characteristic story of recurring gallstone attacks, with known jaundice on two occasions, and a fourth patient (Case 22) had been previously diagnosed as cholelithiasis in this hospital, but operation was deferred. There is thus a total of fifteen cases, or 22 per cent of the series, in which gallbladder disease may fairly be assumed to have existed. Such a percentage is much higher than that usually given as the incidence of cholelithiasis in diabetes. It is true that a group of sixty-eight diabetic patients is too small for statistical purposes. We are inclined to believe, however, that the generally accepted figure of from 6 to 7 per cent, as the incidence of gallstones in diabetes, is far too low. A more logical interpretation of the foregoing figures is possible if we also take into account the age of those patients giving evidence of cholelithiasis. The average age of these patients was 51 years, only one patient being under 45. A justifiable conclusion from such data would seem to be that, in the group of adult diabetic patients, the occurrence of gallstones is frequent. An attempt to determine the exact incidence in diabetic patients over 40 years of age from the series of cases here presented would be injudicious. It may not be unreasonable to suggest, however, that in patients with diabetes mellitus over the age of 30, cholelithiasis may well be an associated feature in at least a fifth of the cases. From our knowledge of the pathology of cholelithiasis it is interesting to consider if this relation to diabetes is an etiologic one. Joslin's figures, which take into account the probable onset of symptoms of cholelithiasis and the subsequent onset of diabetic symptoms, would seem to indicate that gallbladder disease is the cause of the pancreatic disturbance. Findings like those recently reported by Eustis,²⁴ as well as the evidence presented at the beginning of this paper, are also strongly in favor of such a view. In Eustis' thirty-six cases of so-called alimentary glycosuria, fifteen showed cholelithiasis. Six of these cases later presented symptoms of definite diabetes. If the etiologic rôle of gallbladder disease is accepted, we are inclined to agree with Joslin that not only in diabetic, but also in non-diabetic patients, the existence of cholelithiasis is an indication for surgical interference. In the case of nondiabetic patients, surgical intervention may reasonably be advised as a preventive measure against the subsequent development of diabetes.

²⁴ Eustis, A. Relation of Gallbladder Disease to Diabetes, New Orleans M & S J 75 449 (Feb.) 1923

SUMMARY

1 An unselected group of sixty-eight diabetic patients has been examined for evidence of alteration in pancreatic or hepatic activity. Pancreatic enzyme activity was diminished in nearly one-half of the cases. Bile pigment elimination in the duodenal contents was abnormally high in about three-fourths of the cases. In nearly one-third of the cases there were associated enzyme and pigment abnormalities. The greatest alterations in enzyme activity were noted in the lipolytic and proteolytic ferments.

2 These findings are taken to indicate that in diabetes mellitus there is a marked alteration in the external secretory activity of the pancreas and in the hepatic function. The enzyme abnormalities are probably due to associated anatomic and functional changes in the acinar tissue of the pancreas. Undernutrition may play a part in the production of such changes, but it is not the sole cause. Such alterations in pancreatic or liver function may well contribute to the symptomatology of diabetes. It is suggested that the diminution of enzyme activity may result in disturbances due to improper digestion of fat and protein.

3 Undernutrition, of the several variable factors entering into an uncomplicated case of diabetes, evidently places the greatest strain on the liver, and results in striking bile pigment abnormalities. Undernutrition should therefore be avoided, on account of its undesirable effects on liver and pancreatic function.

4 Efficient insulin therapy, with its associated increase in food intake and improvement of tissue function, seems to be associated with a reduction in pancreatic and hepatic abnormalities.

5 Cases of diabetes complicated by pancreatic disease were found to be associated with an increased frequency of pancreatic enzyme disturbance. Sepsis, gangrene, and pancreatitis seemed to be predominating factors in producing an alteration in bile pigment metabolism. All three cases of hemochromatosis showed a reduction in enzyme activity, but no abnormality in pigment elimination.

6 Acidosis produces a marked disturbance of pancreatic enzyme activity and liver function. The improvement in pancreatic and hepatic function, as measured by changes in the enzyme activity and bile pigment elimination, following recovery from acidosis, is very striking, and illustrates the degree to which acidosis affects all bodily functions.

7 Cholelithiasis, as diagnosed by examination of the duodenal sediment, occurred in 19 per cent of the cases in this series. The sediment findings by which such a diagnosis can be made are characteristic, and have been previously described. In addition, several other

patients had histories or operative findings consistent with the diagnosis of gallstones. The average age of this group of cases, constituting 22 per cent of the entire series, was about 51. We believe that the existing figures for the incidence of gallstones in diabetes is far too low. It would not be surprising to find that at least one-fifth of all diabetic patients over 40 have an associated cholelithiasis.

8 In adults, cholelithiasis is probably one of the most important etiologic factors in diabetes mellitus. For this reason, it would seem that surgical intervention in all cases of gallbladder disease, in the absence of other complication, is indicated as a means of preventing the occurrence of diabetes, or of relieving an existing diabetes.

THE RESPIRATORY ORGANS IN HEALTH AND IN DISEASE

XVI A COMPARISON OF VITAL CAPACITY STANDARDS IN THREE
THOUSAND FIVE HUNDRED AND THIRTY-FOUR MALE
UNIVERSITY STUDENTS

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In spite of the large amount of recent work done on the many aspects of the subject of the vital lung capacity, disagreement still exists as to the best choice of standards for predicting the normal capacity of a given individual. The recent interest of thoracic surgeons in the use of vital capacity measurements as an aid to determine surgical risk adds another group to the large number of clinicians already seeking suitable normal standards for use in this work. Hutchinson's¹ pioneer work led to the belief that the standing height was the best measurement on which to base calculations of lung capacity. Peabody and Wentworth² preferred height measurements in their estimations. Lundsgaard and Van Slyke³ advocated the use of certain chest dimensions. West⁴ found surface area most reliable. Dreyer⁵ prepared formulas for estimating vital capacity from height, weight, stem height and chest circumference, and these have been widely used. Dublin⁶ questions the accuracy of all Dreyer's formulas, but finds the one based on weight most nearly correct. It has been established that the lung capacity

¹ From the students' health service and the department of preventive medicine, University of Minnesota.

² Read before the medical staffs of the Lymanhurst School and Hospital for Tuberculosis Children and the Parkview Sanatorium, June 24, 1924.

³ This study was carried out with the aid of a grant from the research fund of the University of Minnesota.

⁴ Hutchinson, J. On the Capacity of the Lungs and on the Respiratory Functions with a View to Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, Tr Med Chir 29:137, 1846.

⁵ Peabody, F W, and Wentworth, J A. Clinical Studies on Respiration, IV, The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch Int Med 20:443 (Sept) 1917.

⁶ Lundsgaard, C, and Van Slyke, D D. Studies of Lung Volume, I, Relation Between Thorax Size and Lung Volume in Normal Adults, J Exper Med 27:65 (Jan) 1918.

⁷ West, H F. Clinical Studies on Respiration, VI, A Comparison of the Various Standards for the Normal Capacity of the Lungs, Arch Int Med 25:306 (March) 1920.

⁸ Dreyer, G, and Hanson, G F. The Assessment of Physical Fitness, New York, Paul B Hoeber, 1921.

⁹ Dublin, L I. The Work of Dreyer in Relation to Life Insurance Examinations, Proc A Life Insurance Medical Directors, 1922, p 202.

varies with sex, age, weight, height, surface area, chest circumference, sitting height, previous occupation, state of health and past history of certain diseases. With so great a number of variables, the difficulty of obtaining enough constants to establish normal variations in lung capacity is apparent. The best opportunity of solving this difficulty appears to lie in observing large numbers of persons in whom the variables can be carefully estimated. The examination of college students seems to offer a good field for this purpose.

In most previous studies of this kind, it has been assumed that all the individuals of the series were normal from the fact that they were not disabled. In a very few instances, vital capacity measurements on large numbers of supposed normal persons have been reported following a cursory physical examination to establish this normality. Hutchinson¹ describes no special method of selecting known normals in his series of 3,000. Schuster² reported vital capacity measurements on 959 Oxford students, but did not detail a method of selecting the normals. Hewlett and Jackson's³ series of 400 students "were active and showed no evident signs of disease." In West's⁴ series, no exceptional measures to exclude abnormals are reported. In our previous series⁵ of 1,304, no attempt was made to select absolute normals, but the range of the vital capacity distributions agreed fairly well with those reported as normals by others. In this series, demonstrable cause for low lung capacity was found in 106 of the 186 students below 90 per cent of normal.

Experience has convinced us that a number of physical factors not uncommon among college students, as well as a history of certain past diseases, will lower the lung capacity. It has been shown,¹⁰ for instance, that a group of persons giving a past history of pleurisy, even without regard to the type of pleurisy, will show a much lower vital capacity as a whole than a group without such history. The frequency with which extensive fibrinous adhesions of the pleural membranes are encountered at necropsy, and the relative infrequency of a past history of pleurisy even in carefully taken histories, illustrates the difficulty of selecting normal individuals in this single instance. Lemon and Moersch¹¹ enumerate many factors not ordinarily associated with pulmonary dis-

7 Schuster, E. First Results from the Oxford Anthropometric Laboratory, *Biometrika* 8 40, 1911

8 Hewlett, A. W., and Jackson, N. R. The Vital Capacity in a Group of College Students, *Arch. Int. Med.* 29 515 (April) 1922

9 Shepard, W. P., and Myers, J. A. A Preliminary Study of the Vital Capacity in College Students, *Journal-Lancet*, 43 355 (July 15) 1923

10 Shepard, W. P. The Effect of Certain Past Diseases on Vital Capacity, *Arch. Int. Med.* 33 185 (Feb.) 1924

11 Lemon, W. S., and Moersch, H. J. Factors Influencing Vital Capacity, *Arch. Int. Med.* 33 136 (Jan.) 1924

ease which tend to lower the vital capacity. Acute respiratory infection, hernia, spinal curvature, unrecognized pulmonary and cardiac disease, overweight, even if slight, and other conditions must be ruled out in selecting a series on which to base standards for vital capacity measurements. Students from China, Japan, India and the Philippines frequently show low vital capacities, in our experience. A lowered vital capacity in Chinese students has been reported by Foster and Hsieh,¹² who suggest a racial factor as another possible variable.

This study was therefore undertaken with a view to comparing the various standards of estimating the vital capacity in a large group of normal young men.

METHODS

During the fall entrance examinations of the last three years at the University of Minnesota, the students' health service has paid particular attention to vital capacity measurements. The complete records of 3,534 male students were available for study. Vital capacity was measured by means of a Sanborn water spirometer. Time was taken to explain the instrument to each student, and to allow from three to five trials before recording the maximum reading. Many students having a low reading without apparent cause were rechecked at a later date, in an effort to secure readings of certain accuracy. All measurements were taken with the student stripped. Chest circumference was measured at the nipple line with the student's back to a mirror so that the tape might be kept horizontal. A measurement was recorded at full inspiration and again at full expiration and the computed mean used for further calculations, after the method of Gray. Sitting height was measured carefully, as described by Dreyer, with the student sitting on a table, the sacrum held firmly against a rule on the wall and the knees drawn up. The condition of the student's health was determined with a fair degree of accuracy by fourteen medical examiners of our own staff, who were given between two and two and one-half hours for each student examined. The occurrence of all important past diseases was noted in the history sheet filled out by the student under competent supervision. By means of Myers'¹³ tables, based on Dreyer's and West's formulas, vital capacity was computed in percentage of normal according to the individual weight, height, chest circumference, sitting height and surface

12 Foster, J. H., and Hsieh, P. L. The Vital Capacity of the Chinese, an Occupational Study, *Arch. Int. Med.* 32:335 (Sept.) 1923.

13 Myers, J. A. Studies on the Respiratory Organs in Health and Disease, VIII, A Method for Quickly Obtaining the Percentage of an Individual's Theoretical Normal Vital Capacity of the Lungs, *Am. Rev. Tuberc.* 7:161 (May) 1923; How Much Should Your Lungs Hold? *J. Outdoor Life*, November, 1923; The Vital Capacity of the Lungs (to be published).

area. Finally, the average of these five determinations was noted. The clerical error in the method employed was less than 2 per cent.

The records were then analyzed with a view to selecting those men in whom no physical defect having a possible bearing on vital capacity could be detected, and those having no past history of pulmonary or cardiac disease. This left only 1,641 who were considered normal. Among those excluded as abnormal and grouped for special study were 376 students giving a history of pneumonia, 333 who were 10 per cent or more overweight for their age and height, according to life insurance standards, 111 giving a history of pleurisy or in whom physical findings of pleurisy

TABLE 1.—*Distribution of Vital Capacity Readings by Various Standards in One Thousand Six Hundred and Forty-One Normal Men University Students*

Percentage of Normal	Weight		Height		Stem Height		Surface Area		Chest Cir- cumference		Average		
	Vital Capacity	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Under 70													
70 to 74				8	0.49	1	0.06	4	0.24	11	0.67		
75 to 79	5	0.31		15	0.92	3	0.18	12	0.73	40	2.44	8	0.49
80 to 84	12	0.73		44	2.68	15	0.92	29	1.77	122	7.43	16	1.10
85 to 89	38	2.32		122	7.43	50	3.05	122	7.43	213	12.96	74	4.51
90 to 94	192	11.70		231	14.08	98	5.97	225	13.70	317	19.30	200	12.20
95 to 99	242	14.75		272	16.57	160	9.75	295	17.98	289	17.60	312	19.00
100 to 104	317	19.33		294	17.91	231	14.05	296	18.08	256	15.60	326	19.88
105 to 109	239	14.56		205	12.49	232	14.12	238	14.20	148	9.02	246	15.00
110 to 114	233	14.20		178	10.85	260	15.83	181	11.02	113	6.88	223	13.60
115 to 119	171	10.42		131	7.98	208	12.35	121	7.87	75	4.57	143	8.72
120 to 124	107	6.52		88	5.36	206	12.55	83	5.06	38	2.32	61	3.72
125 to 129	46	2.80		37	2.25	168	10.22	27	1.64	17	1.03	25	1.52
130 and over 39	238	1.40		16	1.10	14	0.85	13	0.79	2	0.12	7	0.43
Totals	1,641	100.02		1,641	100.11	1,641	99.90	1,641	99.96	1,641	99.94	1,641	100.17

were detected. There were thirty-six students excluded as having history or physical findings, on subsequent examination, of pulmonary tuberculosis. About one third of these had not previously known of the existence of the disease. Thirty-four students showed definite signs of organic heart disease, but were apparently well compensated at the time. These were grouped for special study. A special group was formed of 574 students who were 10 per cent or more underweight, without any evidence of organic defect or past history of pulmonary or cardiac disease. Other conditions encountered and for which the students were excluded as abnormal were acute respiratory infection, hernia, which was frequently found to lower the vital capacity, cicatrices from wounds about the thorax and shoulder girdle, goiter, paralyses, with atrophy of the muscles of the spine or thorax, congenital absence of the pectorals, amputations, developmental abnormalities of the bony thorax, marked spinal curvature, and chronic diseases, such as nephritis.

The ages varied from 15 to 35 years. The average and the modal age was 18. Hutchinson,¹ Wintrich,¹¹ Cornet¹⁵ and Pratt¹⁶ agree that age does not lower vital capacity until from 30 to 35 years are reached.

RESULTS

The incidence distribution of vital capacity readings in the 1,641 students who were considered normal is shown in Table 1 and illustrated in Chart 1. In studying the summation curves in this figure, it will be seen that any agent tending to lower the vital capacity readings shifts the entire curve to the left. From this figure, it will be seen that the computations of vital capacity by means of surface area and standing

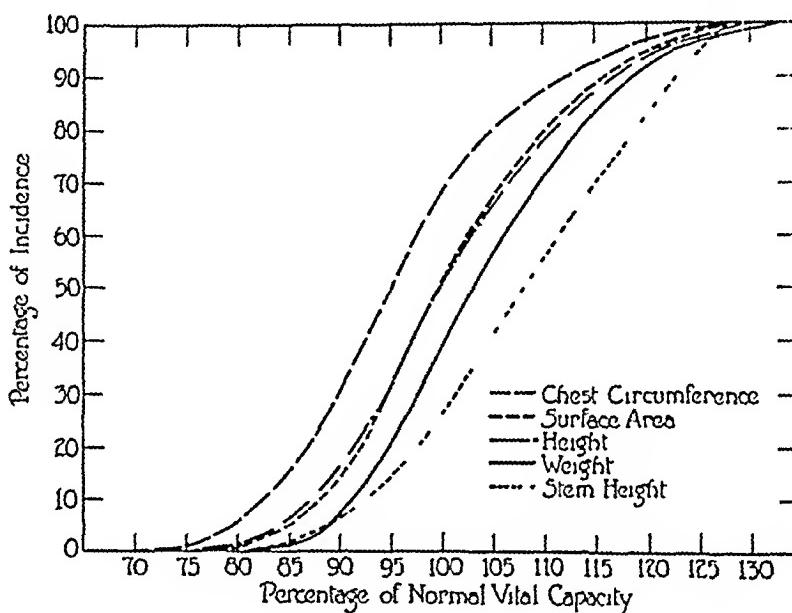


Chart 1.—Vital capacity readings by various standards of 1,641 normal men university students

height almost coincide. The weight formula of Dreyer is practically parallel to the surface area and the height curves and but slightly to the right. Estimations of vital capacity, according to stem height, by the use of the formula employed here give readings too high in comparison to the formulas based on surface area, height and weight. Estimations according to chest circumference, on the other hand, give readings too low. It also will be seen that this group of normal young men showed more vital capacities above 100 per cent normal than below. In Table 1,

14 Wintrich, M A Einleitung zur Darstellung der Krankheiten der Respirationsorgane, Handb d spec Path u Therap Virchow, 1854

15 Cornet, J Einige spirometrische Beobachtungen nebst einem Rückblick auf die bis jetzt aufgestellten methoden zur Bestimmung der physikalischen Vitalcapacitat, Inaugural Dissertation, Munchen, 1884

16 Pratt, J H Long Continued Observations on the Vital Capacity in Health and Heart Disease, Am J M Sc 164:819 (Dec) 1922

nearly 70 per cent of the total number are more than 100 per cent, or normal vital capacity, according to the weight formula, and 35 per cent are more than 110 per cent normal. Only about 3 per cent are below 90 per cent normal vital capacity. It would therefore seem that, when applied to selected normal young men, the vital capacity standards commonly in use are slightly too low. Surface area, standing height and weight standards most nearly coincide. The chest circumference standard is too low and the stem height standard too high compared to the others.

This is in agreement with the findings of West,⁴ who advocated surface area as the best standard on which to estimate lung capacity. In his series of 129, only 5.5 per cent were found to have capacities less than 90 per cent normal. He also stated that Dreyer's weight formula practically agreed with the surface area standard. Hewlett and Jackson⁸ reported better correlation between surface area and vital capacity than between height or weight and vital capacity. In their series of 400, however, 20 per cent of the students fell below 90 per cent normal lung capacity. In our previous series,⁹ using the weight formula of Dreyer and taking what appeared from superficial observation to be normals, 14 per cent fell below 90 per cent normal. In studying the vital capacity in old age with various standards, Myers and Cady¹⁷ found a close agreement between the estimations based on surface area, standing height and weight, while those based on sitting height gave readings 10 per cent higher in men. In studying the vital capacity measurements of 738 college women, Boynton¹⁸ found that the weight and surface area standards nearly coincided, while the stem height estimation gave readings too low and was subject to considerable error. Hewlett and Jackson⁸ suggest that present standards are too low when applied to a selected group of students.

STUDY OF ABNORMALS

In order to emphasize the necessity of careful selection of normals when comparing standards for the estimation of vital capacity, certain of the larger groups of those rejected as abnormal were subjected to special study. The distribution of the vital capacities of these groups is given in Table 2. The average of all five vital capacity determinations (weight, height, surface area, stem height and chest circumference) was used in these groups in order to make the results comparable to those previously reported.¹⁰

17 Myers, J. A., and Cady, L. H. Studies on the Respiratory Organs in Health and Disease, XIII, The Effects of Senility on the Vital Capacity of the Lungs, Am Rev Tuberc 9:57 (March) 1924.

18 Boynton, Ruth E. A Comparison of Normal Standards for the Vital Capacity of the Lungs of Women, Arch Int Med 33:292 (March) 1924.

Three hundred and seventy-six students gave a history of having had pneumonia at some time. Neither the type of pneumonia nor its gravity were determined, but, on the whole, the student's memory of the disease would be better in the more serious cases. The vital capacities of this group are shown in the first column of Table 2, and illustrated by means of summation curves in comparison to the normal in Chart 2. The group, as a whole, shows a slight but definite lowering of the vital capacity throughout.

One hundred and eleven students gave a history of pleurisy. Again, the type and gravity of the disease was undetermined, but, judging from the vital capacities of this group as seen in the second column of Table 2

TABLE 2.—*Distribution of Vital Capacity Readings in Certain Groups Considered Abnormal*

Percentage Pneumonia of Normal	Pneumonia		Pleurisy		Tuberculosis		Cardiac Disease		Overweight		Underweight	
	Vital Capacity Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Under 70					2	5.56						
70 to 74	2	0.53	2	1.80	1	2.78	1	2.94	3	0.90	2	0.55
75 to 79	6	1.60	4	3.60	1	2.78			6	1.80	3	0.52
80 to 84	10	2.66	8	7.20	8	22.20	3	8.83	11	3.30	15	2.62
85 to 89	35	9.31	10	9.00	1	2.78	8	23.50	19	5.70	28	4.88
90 to 94	43	11.43	16	14.40	8	22.20	2	5.63	48	14.40	86	15.00
95 to 99	68	18.10	21	18.90	4	11.10	1	2.94	52	15.61	82	14.50
100 to 104	65	18.10	16	14.40	4	11.10	6	17.65	56	16.80	125	21.80
105 to 109	66	17.55	17	15.30	3	8.83	5	14.70	53	16.50	86	15.00
110 to 114	40	10.64	9	8.10	1	2.78	6	17.65	36	10.80	60	10.45
115 to 119	23	6.65	4	3.60	2	5.56	1	2.94	30	9.00	61	10.63
120 to 124	8	2.13	4	3.60	1	2.78	1	2.94	12	3.60	17	2.96
125 to 129	4	1.09							3	0.90	8	1.40
130 to 134	1	0.27							2	0.60	1	0.18
Totals	376	100.03	111	99.90	36	89.85	34	99.97	333	99.91	574	100.09

and illustrated in Chart 2, the disease was serious enough in the group, as a whole, to cause a definite lowering of the vital capacity. The displacement of the curve to the left is nearly as great as in the small group with tuberculosis described below.

Thirty-six students gave histories or showed physical signs, on subsequent examination, of pulmonary tuberculosis. This included only those with definite physical findings or those who gave an unquestionable history. The effect of this disease on the vital capacity of the group as a whole is shown in the third column of Table 2, and illustrated in comparison with the normal in Chart 3. The lowering of the vital capacity is most pronounced in this group.

Thirty-four students gave unquestionable history, or showed definite physical signs of organic heart disease. In view of the effect of heart disease on vital capacity reported by Ulrich and Nathanson¹⁹ and others,

19 Ulrich, H. L., and Nathanson, M. H. The Vital Capacity of the Lungs in Cardiac Disease, Minnesota Med 4 721 (Dec) 1921

these were grouped for special study. It is noteworthy that all these individuals appeared to be in good health and about one-half the group had never suspected the existence of cardiac disease. In spite of the

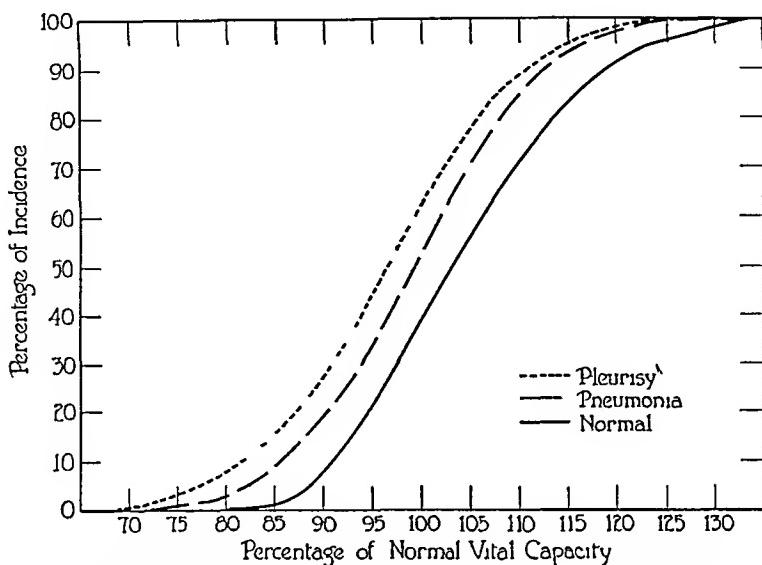


Chart 2—Comparison between vital capacities of normal students and those giving histories of pneumonia and pleurisy

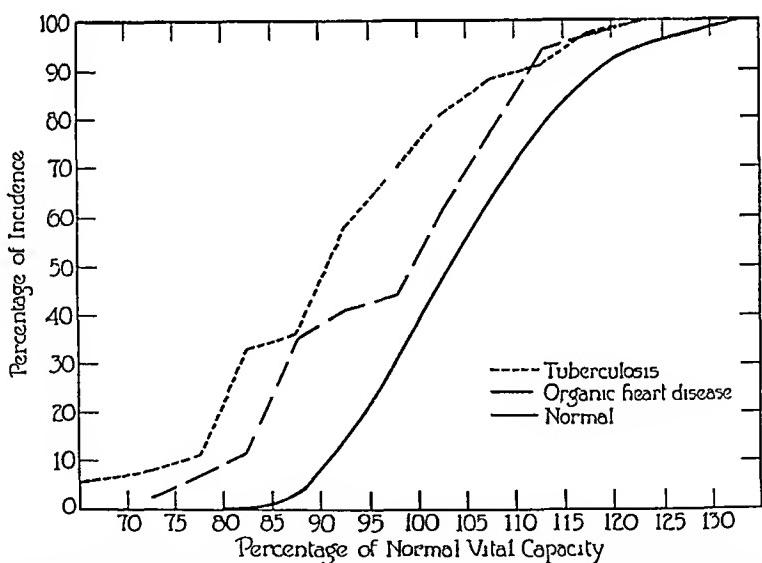


Chart 3—Comparison between vital capacities of normal students and those with histories or physical signs of pulmonary tuberculosis or organic heart disease

absence of symptoms or signs of decompensation or pulmonary congestion, this group, as a whole, showed a marked lowering of the vital capacity (Table 2, Chart 3)

The effect of obesity on the vital capacity has long been recognized. Since the degree of obesity required to lower the vital capacity is ques-

tionable, and it was desired to come well within the margin of safety in selecting the group of normals, all persons who were 10 per cent or more overweight for their age and height, according to life insurance standards, were placed in a special group numbering 333 cases. Table 2 and Chart 4 show that the vital capacity of this group, as a whole, is slightly lowered. Obviously, this method excluded some of the big men who were not truly obese and who had unusually large lung capacity. The occurrence of marked obesity was rare in this age group.

There was a large group of 574 students who were 10 per cent or more underweight, according to insurance standards, but who showed no definite organic defects. Obviously, being 10 per cent underweight is not a serious defect at this age. In some members of the group, how-

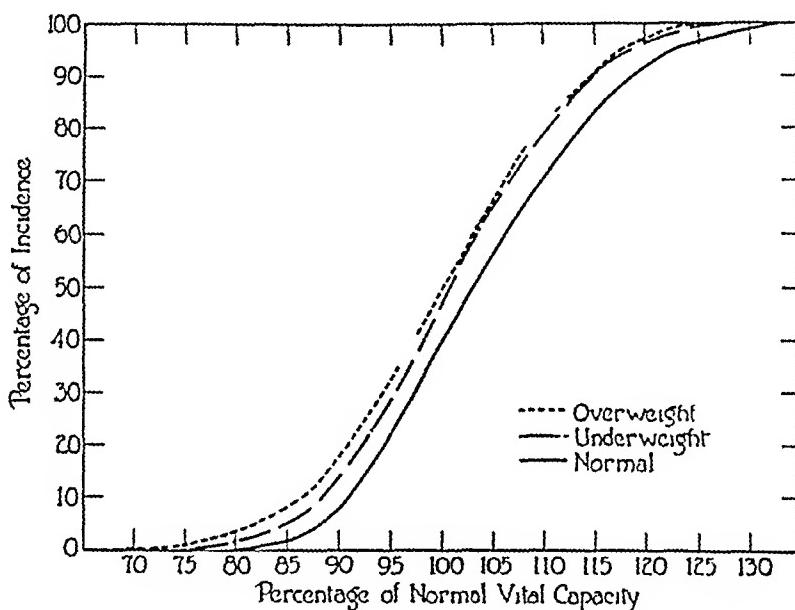


Chart 4.—Comparison between vital capacities of normal students and those 10 per cent or more underweight or overweight.

ever, tuberculosis was suspected, others showed slight evidences of malnutrition, many were of the immature, nonrobust type. Hence, many could not be called normal, and the entire group was excluded. The vital capacities of this group were slightly lowered as shown in Table 2 and Chart 4.

When a curve is plotted to show the vital capacity of all those considered abnormal as compared to a curve for all those considered normal, the curve for abnormalities is slightly but definitely lower throughout. The difference is small enough to bring up the possibility of its being negligible. It is believed, however, that when the size of the series is considered, together with the fact that the division between abnormalities and normals can never be absolute, the importance of using great care in selecting normals as a basis for study is still apparent.

CONCLUSIONS

- 1 When applied to 1,641 carefully selected men university students, the commonly used standards for estimating vital capacity from surface area, height and weight practically coincide
- 2 The estimation based on chest circumference gives readings considerably too low, while that based on sitting height gives readings too high
- 3 When applied to this selected group, all standards give readings too high for a normal distribution
- 4 Great care should be used in selecting normals for purposes of working out standards for the estimation of normal vital capacity

THE PERMEABILITY OF HUMAN BLOOD CELLS
TO CARBON DIOXID AND AMMONIUM
HYDROXID IN SOLUTIONS OF
SAME p_{H}

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INTRODUCTION

The pathology of Bichat, more than a century ago, centred about organs and tissues and that of Virchow about cells, while that of today also concerns the contents of later morphologic units. Little is known of the great variety of complex processes and of obscure changes which occur within cells, but it is recognized that the regulation of their hydrogen ion concentration plays an important rôle in maintaining their normal activity. In contrast to the simplicity of determining the hydrogen ion concentration of the body fluids, it is perhaps impossible to determine it accurately for a part or the whole of living cells. It is a frequent assumption that cells are of the same hydrogen ion concentration as their surrounding medium. That this is not necessarily the case has been shown by Bethe,¹ Warburg,² Harvey, and Jacobs³ from studies made on sea urchin eggs and plant cells. Jacobs has clearly shown that the substances contained in the surrounding fluid, especially carbon dioxide and ammonium salts, have more influence on the p_{H} of structures within cells than does the actual p_{H} of their surrounding medium. The relative permeability of the cells of the human body to carbon dioxide is an important phase in the regulation of respiration, and

* From the medical service of the Collis P Huntington Memorial Hospital of Harvard University. This paper is No 37 of a series of studies on metabolism from the Medical School of Harvard University and allied hospitals. The expenses of this investigation have been defrayed by a grant from the Proctor Fund of the Medical School of Harvard University for the study of chronic diseases.

1 Bethe, A. Die Bedeutung der Elektrolyten für die rhythmischen Bewegungen der Medusen, *Arch f d ges Physiol* **127** 219, 1909

2 Warburg, O. Ueber die Oxydationen in lebenden Zellen nach Versuchen am Seeigeli, *Ztschr f physiol Chem* **66** 305, 1910

3 Harvey, E N. Studies on the Permeability of Cells, *J Exper Zool* **10** 507, 1911

4 Jacobs, M H. The Production of Intracellular Acidity by Neutral and Alkaline Solutions Containing Carbon Dioxide, *Am J Physiol* **53** 457 (Oct) 1920, to What Extent Are the Physiological Effects of Carbon Dioxide Due to Hydrogen Ions? *ibid* **51** 321 (March) 1920, The Influence of Ammonium Salts on Cell Reaction, *J General Physiol* **5** 181 (Nov) 1922 General Cytology, edited by E V Cowdry, Section 3, Chicago, University of Chicago Press, 1924

the question arises whether or not different human cells have the same permeability for carbon dioxide and ammonia. An attempt to answer this question and to determine if Jacobs' results with sea urchin eggs are applicable to living human cells has been the object of the investigations reported here.

METHODS

The observations have been confined to the formed elements of the human blood since they offer conveniently accessible test cells. These observations concern mainly the white blood corpuscles and, to a lesser extent, the platelets. No information could be deduced concerning intracellular changes in the red blood corpuscles except with regard to internal structures, which they contain as a result of their immaturity.

In the first set of observations, a drop of blood was used without any anticoagulant. In the subsequent studies, large numbers of cells were obtained by sedimentation from venous blood to which crystalline sodium citrate was added.

The relatively nontoxic, vitally staining dye, neutral red, was used since it acts as an indicator at the p_H of the blood. The strength of the dye was varied from 0.04 to 0.1 per cent in absolute alcohol in order to stain adequately the varying numbers of cells used.

Chemically clean, dust free, glass slides were flooded with the alcoholic solution of dye, the excess was quickly drained off, and the film allowed to dry. A drop of fresh blood was then taken on a clean glass cover slip, placed on the prepared slide, and sealed with petrolatum. This preparation was then kept in a warm stage at 37.5°C. After five minutes, the intracellular structures within the blood corpuscles which take up neutral red became uniformly stained. The influence on the cells of three solutions of the same p_H , but of different composition, was then tested. These three solutions were the same as those used by Jacobs,⁴ and were prepared as follows:

1 Half molar sodium chloride was brought to p_H 7.4 with a trace of sodium bicarbonate.

2 Half molar ammonium chloride was brought to p_H 7.4 with ammonium hydroxide.

3 Half molar sodium bicarbonate was brought to p_H 7.4 with carbon dioxide gas.

These solutions were drawn under the cover glass and mixed with the blood, according to the requirements of the different experiments. In the group of experiments with masses of cells, larger quantities of the solutions were mixed with the "leukocyte cream" in test tubes.

All determinations of the hydrogen ion concentrations of fluids were made by color comparison with standard buffer solutions (prepared

according to the method of Palitzsch⁵) to which brom-thymol blue was added as an indicator

The different experiments were repeated numerous times in order to verify the correctness of the observations

OBSERVATIONS

1 *The Changes Within the Cells*—An excellent study of blood cells stained with vital dyes has been made by Sabin,⁶ so that only brief reference will be given here to the phenomena observed

When fresh blood is stained with neutral red, the polymorphonuclear neutrophil leukocytes, within the course of a few minutes, show red staining particles that are definite, constant and characteristic structures within the cytoplasm. It is not possible to tell definitely whether these vitally staining granules are the same as those that become colored in a fixed preparation with Wright's stain. These vitally stained particles are constantly streaming through the cytoplasm as the cell puts out its blunt pseudopodia. If the cell is injured, it ceases to move and the vitally staining granules take on brownian movement. If the cells die, their nuclei, which have previously been unstained, take up the dye, while the vitally staining granules in the cytoplasm lose much of their red color. The behavior of all other white blood cells is similar to that of the polymorphonuclear neutrophil leukocytes, and the number of red staining particles apparently varies with the number of granules observed in similar cells stained with Wright's stain.

Characteristically, the platelets contain several intracellular structures that stain brilliantly with neutral red. When the platelets are dead, the dye may permeate diffusely through their protoplasm, giving it the appearance of ground glass.

In a preparation of fresh blood stained with neutral red, there may be seen only a very faint staining of the mature red blood corpuscles. Normal immature red blood corpuscles may contain nuclei, reticulum, and granules (Isaacs⁷), and of these structures in the living cell only the reticulum stains with neutral red. This staining of the reticular substance was observed many times, and even the smallest portion quickly takes up the dye.

The fresh vitally stained specimens of blood were each subjected to one of the three solutions previously described, and their effect was

5 Palitzsch, S., quoted by Clark, W. M. *The Determination of Hydrogen Ions*, Baltimore, Williams & Wilkins Co., 1920, p. 85.

6 Sabin, F. R. *Studies of Living Human Blood Cells*, Bull. Johns Hopkins Hosp. 34, 277 (Sept.) 1923.

7 Isaacs, R. *Properties of Young Erythrocytes in Relation to Agglutination, and Their Behavior in Hemorrhage and Transfusion*, Arch. Int. Med. 33, 93 (Feb.) 1924.

noted on the vitally staining intracellular structures. In Table 1 are shown the changes caused by the solutions in the color of the stained particles of living and dead polymorphonuclear neutrophil leukocytes and platelets, in the stained nucleus and partially stained cytoplasm of these cells when dead, and in the cytoplasm and reticulum of nucleated and nonnucleated erythrocytes.

The solution of sodium chlorid brought to p_H 7.4 with a trace of sodium bicarbonate caused no change in the color of any stained intracellular structures. The table shows, however, that when a living leukocyte is subjected to the solution at p_H 7.4 which contains ammonia, the reaction of the vitally stained intracellular particles becomes alkaline, while if the surrounding solution, also at p_H 7.4, contains carbon dioxide

TABLE 1.—Effect of Three Different Solutions of Same p_H on Structures of Blood Cells That Stain Vitally with Neutral Red

Type of Cell Structure	Solution 1 Half Molar Sodium Chlorid and Trace Sodium Bicarbonate p_H 7.4	Solution 2 Half Molar Ammonium Chlorid and Ammonium Hydroxid p_H 7.4	Solution 3 Half Molar Sodium Bicarbonate and Carbon Dioxide p_H 7.4
Cytoplasmic granules of living polymorphonuclear neutrophil leukocytes and blood platelets	No change	Change to yellow, alkaline reaction	Change to scarlet acid reaction
Nucleus and cytoplasmic granules of dead polymorphonuclear neutrophil leukocytes and blood platelets	No change	Change to scarlet, acid reaction	Change to yellow, alkaline reaction
Cytoplasm of nucleated and nonnucleated erythrocytes	No detectable change	No detectable change	No detectable change
Reticulum of nucleated and nonnucleated erythrocytes	No change	Change to scarlet, acid reaction	Change to yellow alkaline reaction

the reaction of these granules becomes on the acid side of neutrality. The stained structures in the dead leukocytes and the reticulum of the immature red blood corpuscles, on the other hand, have an opposite reaction to the latter two solutions to that of structures within the living white corpuscles.

Observations made on polymorphonuclear eosinophil and basophil leukocytes, large mononuclear leukocytes, lymphocytes, and all forms of immature myeloid and lymphoid cells from cases of myelogenous and lymphatic leukemia showed that the vitally staining structures which they contain reacted in the same way to the test solutions as did the stained granules of the living neutrophilic leukocytes. The mechanical difficulties of exposing all the cells to the test solutions at the same moment were such that it was impossible to make any accurate quantitative comparisons on the time required to change the color of the stained particles. The impression was gained that the lymphocytes not only stained more rapidly with the dye but also reacted more quickly to the

test solutions than did the other white blood corpuscles. It is worthy of note that the behavior of all forms of white blood corpuscles to the test solutions is strikingly similar irrespective of either their morphologic differentiation or their degree of maturity.

The stained particles in the blood platelets reacted in the same fashion as the vitally stained granules of the living leukocytes, which is to be expected in view of the fact that the platelets are detached cytoplasmic fragments.

Changes in the color of adult erythrocytes when subjected to neutral red are so slight that they do not serve to indicate alterations in the hydrogen ion concentration. The adult red blood corpuscles are such important units in the scheme of hemal transportation that many attempts were made to introduce an indicator into their protoplasm for the purpose of observing their reaction. Numerous vital dyes were tried but, unfortunately, none sufficed for the purpose.

That the reticulum of the nucleated and nonnucleated erythrocytes should react to the test solutions in the same way as the stained structures of the dead leukocytes may be taken as evidence in favor of the view set forth by Key,⁸ that the reticulum is an inactive substance which is precipitated by the action of certain vital stains. However, this observation may have no bearing on the nature of the reticular substance for the phenomenon may be due to a different character of the cell membrane of the erythrocytes from that of the living white blood corpuscles. Cytologically, the erythrocytes often are not considered as true cells, hence the semipermeable properties of their membranes may not be comparable to those of other living cells.

2 The Changes in the Surrounding Medium.—It has been observed that when blood cells stained with neutral red are subjected to solutions of the same p_{H} , but of different composition, the color reaction of those intracellular structures which take up the dye may be changed. It is logical to assume that the reaction of the surrounding medium should become altered as a result of the loss of those substances which penetrate the cells. The following experiment was devised to determine if this change could be demonstrated.

One cubic centimeter of the "leukocyte cream" from blood obtained from patients with chronic leukemia was placed in a warm glass centrifuge tube. Two cubic centimeters of the solution to be tested were mixed with these living cells. This preparation was at once centrifugated for three minutes at 1,000 revolutions per minute and the p_{H} of the resulting supernatant fluid was determined immediately.

⁸ Key, J. A. Studies on Erythrocytes, with Special Reference to Reticulum, Polychromatophilia and Mitochondria, *Arch. Int. Med.* **28** 511 (Nov.) 1921.

This experiment was repeatedly done with each of the three test solutions, using white cells removed from the blood both soon and some time after its withdrawal from the body.

The results obtained were always consistent with those given in Table 2.

The time which elapses between the withdrawal of the blood from the body and the separation of the white corpuscles influences the results. When the cells are separated from the blood by centrifugation as soon as possible after its removal from the blood stream and a uniform number immediately mixed with each of the three test solutions, the p_H of Solutions 1 and 3 is unchanged, while that of Solution 2 is slightly decreased. On the other hand, when the whole blood stands in an incubator at 37.5°C for approximately two hours, until the cells have settled out, the solutions then, after contact with the cells, show a decrease in the p_H of Solutions 1 and 2 while that of Solution 3 remains

TABLE 2—Changes in the p_H of the Test Solutions Surrounding the Living White Blood Corpuscles

Interval Between the Withdrawal of the Blood from the Body and the Separation of the White Cells	Solution 1 Half Molar Sodium Chlorid and Trace Sodium Bicarbonate p_H 7.4	Solution 2 Half Molar Ammonium Chlorid and Ammonium Hydroxid p_H 7.4	Solution 3 Half Molar Sodium Bicarbonate and Carbon Dioxid p_H 7.4
About 8 minutes	p_H 7.4	p_H 7.1	p_H 7.4
About 2 hours	p_H 6.8	p_H 6.8	p_H 7.4

unchanged. It is probable that the products of cellular metabolism collect in the cells, on standing, to a sufficient extent to cause the variation in the findings.

It will be recalled that the vitally stained particles in the living leukocytes were observed to have an acid reaction when subjected to the solution containing carbon dioxide. Apparently, this solution has lost acid which has penetrated the cells, and yet, after contact with large numbers of cells, no change in its p_H was demonstrated. In contradistinction, the penetration of ammonia from Solution 2 into the white blood corpuscles results in a demonstrable increase in acidity of this solution, and this acidity is more pronounced if the cells are sedimented by standing in an incubator. Solution 1 contains no substances capable of rapid penetration into the cells, and there is no change in its p_H other than that caused by the condition of the cells. These results can be explained by recognizing the difference in buffer properties of the three test solutions. Solution 1 (sodium chlorid plus sodium bicarbonate) changes its p_H with great ease on the addition of acid, Solution 3 (sodium bicarbonate plus carbon dioxide) resists strongly change of p_H .

by the addition of acid, while Solution 2 (ammonium chloride plus ammonium hydroxide) acts intermediately between these two. It seemed reasonable that since these solutions differ in their buffer properties, any changes which occurred as a result of the migration of ions into the cells might be demonstrated by titrating the solutions before and after they had been mixed with leukocytes. Consequently, each of the solutions was titrated to $p_{H_2} 6.6$ with hundredth normal hydrochloric acid using phenol red as an indicator, both before and after the solutions had been in contact, for about four minutes, with white blood cells obtained as soon as possible from patients with leukemia. The results shown in Table 3 were obtained in each of several successive observations with cells of both lymphoid and myeloid origin.

TABLE 3.—Amount of Hundredth Normal Hydrochloric Acid Required to Titrate 1 cc. of Test Solution to $p_{H_2} 6.6$ Using Phenol Red as an Indicator

Conditions of Experiment	Solution 1 Half Molal Sodium Chloride and Trace Sodium Bicarbonate $p_{H_2} 7.4$	Solution 2 Half Molal Ammonium Chloride and Ammonium Hydroxide $p_{H_2} 7.4$	Solution 3 Half Molal Sodium Bicarbonate and Carbon Dioxide $p_{H_2} 7.4$
Before mixing with the "leuko cyte cream"	1.2 cc N/100 hydrochloric acid	1.75 cc N/100 hydrochloric acid	4.1 cc N/100 hydrochloric acid
After mixing with the leuko cyte cream'	1.1 cc N/100 hydrochloric acid	0.8 cc N/100 hydrochloric acid	4.9 cc N/100 hydrochloric acid

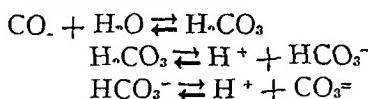
The results shown in Table 3 not only illustrate the relative buffer properties of the test solutions, but also give proof of the fact that the surrounding medium changes its titratable acidity when there is a change of color reaction of stained intracellular structures. It will be observed that there is little or no change in the solution containing sodium chloride and sodium bicarbonate after it has been mixed with white blood cells nor does this solution cause any detectable change in the color of those intracellular particles which stain vitally with neutral red. The solution which contains ammonia causes the vitally stained particles of living cells to become yellow, for it loses alkali when in contact with cells, and, hence, less acid is required to bring it to a p_{H_2} of 6.6. Finally, the penetration of carbon dioxide into the living leukocytes causes their vitally stained structures to change from red to scarlet, and leaves the third solution more alkaline, and, as a result, more hundredth normal hydrochloric acid is required to bring it to a p_{H_2} of 6.6.

COMMENT

The experiments demonstrate for human blood cells what Jacobs¹ has shown holds true for sea urchin eggs and plant cells, namely, that intracellular acidity and alkalinity may be produced by solutions of the

same p_H but of different composition. No distinct differences could be detected between any of the known forms of mature and immature living white blood corpuscles or blood platelets in their reaction to the three solutions. However, the reaction for dead cells and for the reticulum of erythrocytes was the reverse of that for living white blood cells.

It is presumed that the presence of carbon dioxide and ammonia in these solutions is responsible for the changes that occur. In all biologic phenomena involving carbon dioxide and ammonia for their production, there is always sufficient water present to bring about the dissociation of these substances. Carbon dioxide in aqueous solution behaves as a weak acid for its dissociates as follows:



The partial hydrolysis of the acid salt ammonium chloride in aqueous solution produces ammonium hydroxide, and, in the test solution used, a trace of the latter is added to secure a reaction for the whole of p_H 7.4. Sodium hydroxide, aside from the equilibrium which it maintains with ammonia, dissociates into ammonium and hydroxide ions. There is insufficient evidence at hand to determine definitely what forms of carbon dioxide and ammonia penetrate the cells and what forms cause the changes observed. Therefore, when the terms carbon dioxide and ammonia are used here, they should be interpreted in their broadest sense to include any of their dissociation products in aqueous solutions.

The experiments that have been performed demonstrate not only that the p_H of intracellular structures, as shown by their color changes, may be changed in either direction or unchanged by solutions of the same p_H , but they also show that the change of reaction of these solutions is in the opposite direction to those within the cells. The solutions become more acid when the stained intracellular particles become alkaline and vice versa. This phenomenon of the cellular reaction being opposite to that of the surrounding medium occurs in the physiologic processes of the production of gastric juice and the secretion of urine. Bernard,⁹ by the use of the Prussian blue reaction, demonstrated that the gastric glands were not acid. Harvey and Bensley,¹⁰ by means of the injection of vital dyes, and Chambers,¹¹ by microdissection studies,

⁹ Bernard, Claude. *Leçons sur les propriétés physiologiques des liquides de l'organisme*, Paris, 1859, p. 375.

¹⁰ Harvey, B. C. H., and Bensley, R. R. Upon the Formation of Hydrochloric Acid in the Foveolae and on the Surface of the Gastric Mucous Membrane and the Nonacid Character of the Contents of Gland Cells and Lumina, Biol Bull 23: 225, 1912.

¹¹ Chambers, R. Microdissection Studies on the Physical Properties of Protoplasm, Lancet Clinic 123: 363, 1915.

have shown that the parietal cells of the gastric glands are alkaline when there is an active production of an acid gastric juice. Stieglitz¹² has recently demonstrated that the cells of the kidney tubules, which are aiding in the secretion of an acid urine and are nourished by blood which is nearly neutral, are themselves alkaline in reaction. This difference in reaction between cells and fluids may be an important phase of the mechanism for the control of the hydrogen ion concentration of the organism. In any event, it may be conclusively stated that the presumption that the p_H of the surrounding medium is always the same as the p_H of the cells is erroneous and untenable.

The results that have been obtained indicate that carbon dioxide and ammonia penetrate human blood cells more easily than do the other substances present in the solutions. This is in accord with previous knowledge concerning these substances. It is probable that, since carbon dioxide and ammonia are formed in the body, the physiologic results which they produce, in part, may be attributed to their property of permeability. In no way is it wished to convey the idea that by demonstrating a change of p_H of the vitally staining structures in blood cells, there has been demonstrated a change of p_H of the cytoplasm. The living cytoplasm, as it is ordinarily conceived, contains amphoteric electrolytes, which would resist change in p_H . Moreover, as Fischell,¹³ M R Lewis,¹⁴ W H Lewis¹⁵ and Prigosen¹⁶ have maintained, neutral red furnishes data only in regard to certain preformed bodies existing within the cells. That these stained particles are chemically fixed and are not a part of the living cytoplasm has been put forth by W H Lewis¹⁵ and by Bechold.¹⁷ The statement of M R Lewis,¹⁴ that "it is impossible, so far as I know, to determine the hydrogen ion concentration of the living cell," clearly and correctly expresses the difficulties of the problem. This does not detract from the importance of the fact that one cannot predict the p_H of structures within the cell from the p_H .

12 Stieglitz, E J Histologic Hydrogen Ion Studies of the Kidney, Arch Int Med **33** 483 (April) 1924

13 Fischel, A Untersuchungen über vitale Farbung, Anat Hefte **16** 415, 1901

14 Lewis, M R The Effect of Certain Vital Stains Upon the Development of the Eggs of *Cerebratulus lacteus*, *Echinorachinus parma* and *Lophius piscatorius*, Anat Rec **13** 21, 1917 Reversible Gelation in Living Cells, Bull Johns Hopkins Hosp **34** 373 (Nov) 1923

15 Lewis, W H Degeneration Granules and Vacuoles in the Fibroblasts of Chick Embryos Cultivated in Vitro, Bull Johns Hopkins Hosp **30** 81 (April) 1919

16 Prigosen, R E The Formation of Vacuoles and Neutral Red Granules in Connective Tissue Cells and Blood Cells Observed Under Abnormal Conditions, Bull Johns Hopkins Hosp **32** 206 (June) 1921

17 Bechold, H Colloids in Biology and Medicine, Trans by J G M Bullowa, New York, D Van Nostrand Company, 1919

of the surrounding medium. For though these vitally staining constituents may not be a part of the living cytoplasm, yet they are contained in it, and any substance which penetrates the cell membrane and changes their p_H must first pass through the cytoplasm.

CONCLUSIONS

- 1 The formed elements of the human blood are freely permeable to carbon dioxide and ammonium hydroxid.
- 2 The intracellular structures of living white blood corpuscles and blood platelets which stain vitally with neutral red may be made acid, alkaline, or remain essentially neutral by surrounding solutions with a p_H of 7.4.
- 3 These same solutions cause the reaction of the stained intracellular structures of dead white blood cells and the reticulum of erythrocytes to be the reverse of that produced in the living leukocytes.
- 4 Changes in the reaction within the cells are accompanied by opposite changes in the surrounding medium.

THE INFLUENCE OF FOOD INTAKE ON THE
ENZYMATIC CONCENTRATION OF HUMAN
INTESTINAL CONTENTS OBTAINED
FROM A DUODENAL FISTULA

DANIEL N SILVERMAN, M D

AND

WILLY DENIS, PH D

NFW ORLIANS

The rapidly increasing use of the duodenal tube has also greatly increased the need of practical chemical methods for the examination of duodenal contents, and as a result several systems have been described¹. Of these methods, we have had most experience with the technic of McClure, Wetmore and Reynolds,¹ which was selected for this purpose because it appeared to us to be based on methods which had been carefully and scientifically tested out in other lines of work.

Two points operate against the practical application of the methods of examination of duodenal contents described by McClure and his collaborators. One of these is that the reagents used in the preparation of the substrate either are difficult to secure or are of varying composition. These authors recommend for this purpose an emulsion of cotton-seed oil prepared by the Walker-Gordon Company of Boston, a preparation of paracasein (the soluble casein of Van Slyke and Bosworth) which, as far as we have been able to learn, cannot be bought on the market, but must be prepared in the laboratory, and soluble starch, which must be selected with the view of obtaining a preparation containing a minimum amount of reducing bodies. We have used throughout our work an emulsion of cottonseed oil secured from the Walker-Gordon Company, but have replaced the soluble casein (paracasein) recommended by a high grade of casein (Pfundstiehl's highest purity) and the soluble starch by the ordinary corn starch prepared by boiling 2 gm of this substance with 100 cc of distilled water for half an hour, at the end of this period the starch paste is cooled, made up to the original volume (100 cc) and mixed with 100 cc of McClure's 0.2 molal phosphate mixture of $p_{H} 8.4$.

* From the Department of Medicine and the Laboratory of Physiologic Chemistry of the Tulane University of Louisiana School of Medicine

¹ McClure, C W, Wetmore, A S, and Reynolds, L New Methods for Estimating Enzymatic Activity of Duodenal Contents of Normal Man, Arch Int Med 27 706 (June) 1921

The second objection to the practical application of duodenal analysis is the fact that McClure² recommends the use of a cream meal (50 cc of 20 per cent cream) to be given by mouth after the duodenal tube has been passed. This procedure is often difficult of application as cream is frequently not available in hospitals except on special order, and its administration adds another rather troublesome detail even in office practice.

The use of the cream meal was recommended because it was found that the ingestion of fat apparently caused the flow of a juice richer in enzymes than that obtained after the use of carbohydrate or protein and it was believed by McClure and his collaborators that the examination of such a secretion, representing a fluid of maximum digestive power for the individual under examination, was of greater diagnostic value than the analysis of the secretion obtained from the fasting subject.

We have recently had the opportunity of collecting and examining a considerable number of specimens of duodenal juice from a patient with a duodenal fistula, from whom it was possible to obtain liberal portions of the duodenal contents by means of a syringe, the tip of which could be inserted through the fistulous opening. In view of the scarcity of published data regarding the enzymatic concentration of normal duodenal contents, we have felt that the publication of our results might furnish material of interest to workers in this field.

REPORT OF CASE

The patient, a negro laborer, aged 23, was an inmate of the New Orleans Charity Hospital, to which institution he had been admitted, Dec 21, 1923, suffering from an injury caused by a pistol bullet which had entered the right side immediately below the costal border. On operation, which was performed by Dr E L Irwin, a few hours after admission, repair was made of three perforations of the colon, and, as it was found that the projectile had made exit immediately posterior to the gallbladder, perforating this organ at its attachment to the liver, a cholecystostomy also was performed. After the operation, the patient made satisfactory progress for sixteen days, when, during a fit of coughing, the suture line gave way. In an emergency operation, the abdominal wound was again closed. Progress now continued to be satisfactory until Feb 22, 1924, when it was noted that a fistulous opening had appeared in the upper third of the abdominal wound. Exploration of this fistulous opening, by Dr Irwin, gave definite evidence of its duodenal origin.

After the third operation, the patient continued to make satisfactory progress, and, in spite of the persistence of the fistula, he gained rapidly in weight and strength. As judged by the amount and quality of the food consumed, he was apparently possessed of unusually good digestive powers, and as his cooperation was easily secured, he was found to be an excellent experimental subject.

² McClure, C W, and Wetmore, A S. Studies in Pancreatic Function. Enzyme Concentration of Duodenal Contents After Ingestion of Pure Food-stuffs and Food Mixtures by Normal Man, Boston M & S J 187 882-895 (Dec 14) 1922.

EXPERIMENTS

All experiments were performed in the forenoon when the patient was resting quietly in bed. As the secretion flowed more or less continuously from the fistula, it was necessary to have an assistant at hand to mop up the overflow with gauze. When a specimen was desired, the tip of an ordinary glass syringe to which had been attached a short piece of rubber tubing was inserted just within the opening of the fistula, and a sample sufficiently large for the determination of the enzymatic concentration and the p_H (by the electrometric method) was secured in a period of one to two minutes.

In every experiment, the patient was first observed in the fasting condition (from eighteen to nineteen hours after the last meal) and after a sufficient number of samples of fasting contents had been obtained, he was then fed by mouth definite amounts of relatively simple foodstuffs.

EXPERIMENT 1—Effect of Milk Ingestion on Duodenal Enzymes, Enzymatic Concentration

Time, April 3, 1924	Lipolytic				p_H	Remarks
	Amylo lytic in Mg Glucose	Tenth Normal Sodium Hydroxyl	Proteo lytic in Mg Nonprotein Nitrogen			
9:38 a.m.	2.6	0	4.6	6.80		Fasting about eighteen hours
10:00	2.2	0	4.6	6.66		Fasting
10:04	2.2	0	5	6.60		Fasting, 200 cc. of milk given at 10:03, and 200 cc. at 10:37
11:08	2.0	0.2	5.3	7.08		First curds appeared in fistula liquid at 10:46

EXPERIMENT 2—Effect of Cream Ingestion on Duodenal Enzymes, Enzymatic Concentration

Time, April 6, 1924	Lipolytic				p_H	Remarks
	Amylo lytic in Mg Glucose	Tenth Normal Sodium Hydroxyl	Proteo lytic in Mg Nonprotein Nitrogen			
10:22 a.m.	1.37	0.1	1.6	7.26		Fasting about nineteen hours
10:53	2	0	3.3	7.31		200 cc. of 20 per cent cream given at 10:27
11:13	1.4	1.1	3.3	7.5		A second 200 cc. portion of cream given at 10:57
11:43	1.6	0.4	2.9	6.94		Curds from cream appeared in the fistula fluid at 10:58

EXPERIMENT 3—Effect of Egg Albumin Ingestion on Duodenal Enzymes, Enzymatic Concentration

Time, April 8, 1924	Lipolytic				p_H	Remarks
	Amylo lytic in Mg Glucose	Tenth Normal Sodium Hydroxyl	Proteo lytic in Mg Nonprotein Nitrogen			
9:25 a.m.	2.4	0	4.4	6.81		Fasting about eighteen hours
10:30	5	0	5.1	7.65		At 9:45, fed eight egg whites and one yolk boiled two minutes, and a small amount of sodium chloride
11:05	5	1.5	8.7	6.50		Subject sleeping
11:26	2.8	1.3	7.6	6.42		Subject awake

EXPERIMENT 4.—Effect of Starch Ingestion on Duodenal Enzymes, Enzymatic Concentration

Time, April 17, 1924	Amylo- lase in Mg	Lipolytic		Proteo- lytic Normal in Mg	p_H	Remarks
		in Cc	Tenth			
9 50 a m	3 6	0 3	3 1	6 71		
10 14	3	0 1	5 7	7 17	Started eating 153 gm of arrowroot biscuit	
10 35	1 7	0 1	3 4	7 44	Finished crackers and drank 200 c c of water, at 10 33, crackers appeared in the secretion	
10 53	2 26	0 2	6	7 45	Patient asleep	
11 36	3	0 6	6 2	6 75		

SUMMARY

The influence on the pancreatic secretion of different foodstuffs taken by mouth has been demonstrated in the foregoing experiments, these observations were made under such conditions that there was no interference with the gastric function, which must necessarily come with the use of a duodenal tube.

The fasting duodenal fluid was collected and the enzyme concentration determined as a working basis in each experiment. The p_H of each specimen analyzed was always recorded.

The effect of ingesting a mixture of protein, fat and carbohydrate, in the form of 400 c c of milk, taken in two equal portions one-half hour apart, is a stimulation of the protease and lipase (Experiment 1). This increase in proteolytic and lipolytic activity was noted one-half hour after the subject took the last portion of milk.

The ingestion of fat in the form of cream, in two portions of 200 c c each, one-half hour apart, brought about a very distinct stimulation of the amylase and the protease within twenty-six minutes after taking the first portion. About twenty minutes later (sixteen minutes after the second portion of cream), there was noted a marked increase in the lipase concentration.

The ingestion of protein and a very small amount of fat, in the form of eight egg whites and one yolk boiled two minutes, was productive of the most striking results as yet observed. All three of the pancreatic enzymes assumed the maximum concentrations noted in any of the experiments made on this subject. In one hour and seventeen minutes after the eggs were taken, both the amylase and the protease had almost doubled their concentrations, whereas the lipolytic activity rose from 0 to 1 5 c c.

The ingestion of the starch in the form of arrowroot biscuits, which proved very appetizing to the patient, did not, in spite of the psychologic effect show any stimulation on the production of amylase and but little more on the protease.

CONCLUSIONS

Finally, it may be said that it is not our desire to draw any general conclusions from these experiments, however, the fact that this case offered an exceptional opportunity for studies of the enzymatic activity of the duodenal contents, collected without the possibility of disturbed normal function produced by the presence of a duodenal tube, accounts for our report of results that are very suggestive.

THE ELECTROCARDIOGRAM AS AN AID IN THE DIAGNOSIS OF ADHESIVE PERICARDIAL MEDIASTINITIS¹

FRANCIS R DIEUAIDE, MD

BALTIMORE

Since the early days of the application of the string galvanometer to the study of the human heart, it has been known that in normal persons, on changing the position of the subject,¹ there is a change in the form of the record as secured in the three leads. This is especially prominent in patients with cardiac disease. It is best seen on turning the individual in the reclining position from one side to the other. It was thought that this phenomenon might be of practical use in the diagnosis of adhesive pericardial mediastinitis, of which we have no thoroughly reliable clinical sign. Normal persons and patients have been examined from time to time during the last three years to test this possibility.

The change in the form of the electrocardiogram affects all of the waves present to a greater or lesser degree, but is most easily seen in the Q-R-S group. All three leads are affected, but usually only two leads show marked alteration, and the third may remain to casual inspection essentially the same. Those which show conspicuous variation are normally Leads I and III. In electrocardiograms of abnormalities, other combinations of leads may show the prominent alterations, depending on the position of the electrical axis.² For example, with so-called right ventricular preponderance (which might better be called predominance of the dextrogram), Leads I and II present the marked deviations.

The extent of the shift may be calculated mathematically in terms of the angle α of the electrical axis.³ For this purpose, at least two, and preferably three, leads must be taken synchronously, with the proper precautions.⁴ The values of the angle α are then determined for any selected instant in the electrocardiographic records secured in the two positions. As far as possible, the same instant in the cardiac cycle should be used in comparing records taken of an individual in different

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1 Einthoven, W Lancet **1** 853, 1912

2 Carter, E P, and Dieuaide, F R Bull Johns Hopkins Hosp **32** 219 (July) 1921

3 Dieuaide, F R Determination and Significance of Electrical Axis of Human Heart, Arch Int Med **27** 558 (May) 1921

4 Einthoven, W, Bergansius, F L, and Bijtel, J Arch f d ges Physiol **164** 167 1916 Cohn, A E Heart **9** 311, 1922

positions or at different times. It is not necessarily the case that the peak of R, for example, in a given lead occurs at the same instant under these circumstances, especially in electrocardiograms of diseased hearts. Hence, the use of such a criterion may give data which should not be compared. The best basis for comparing electrical axes is to take a certain instant after the earliest Q-R-S deviation in whatever lead that may occur.

Because of the relatively small number of cases which have been available for study we have not thought it desirable to attempt to fix

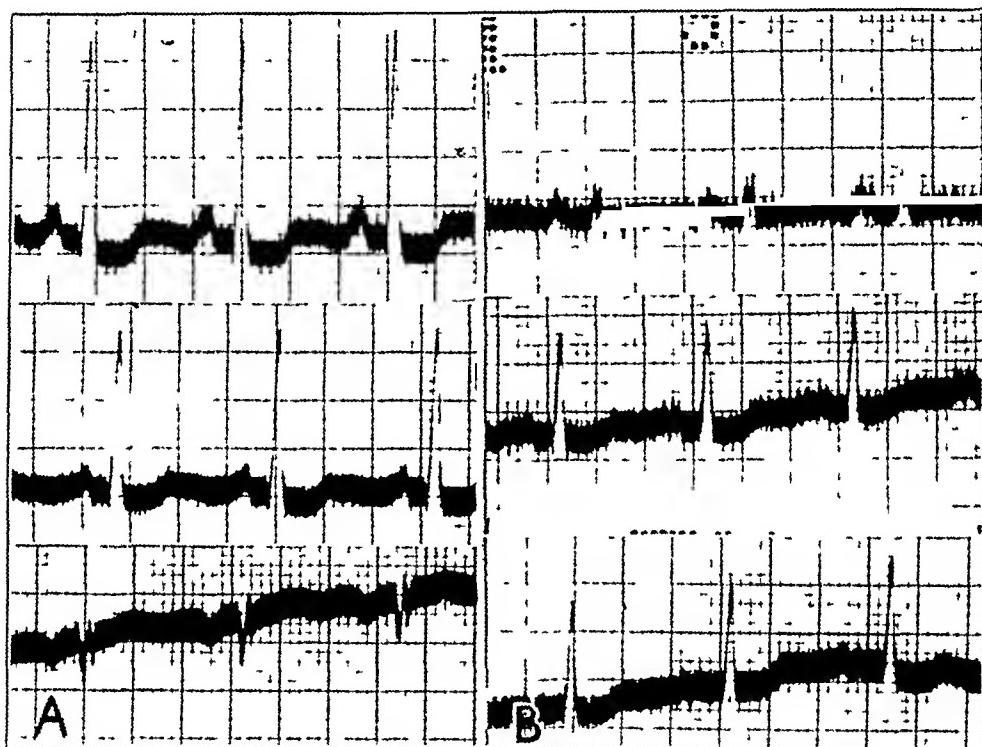


Fig 1 (Case 2)—*A*, patient on right side, *B*, on left side, marked change in form of Leads I and III.

limits for the normal shift on changing the position of the subject, nor have we consistently determined the exact degree of shift in the pathologic cases, since the use of the mathematical determination of the electrical axis would greatly limit the availability of the procedure. We have, therefore, confined our interest to the cases in which, on careful inspection, there is practically no change in the form of the electrocardiogram.

In most instances, our procedure has been to take the three leads with the patient lying well over on his right side, then to turn the patient so that he lies on his left side and repeat the process. In many cases, respiration has such a marked effect on the form of the waves that a record of the respiratory phases should be made syn-

chronously. This may be readily done by means of the ordinary pneumograph with a tambour and lever set before the camera or by the spirometer method of Cohn.⁴ Where it was necessary, we have used the pneumograph. Standardization of the galvanometer string should be carefully carried out and indicated on the record. If the standardization is not exact in the various leads and positions, the measurements may be corrected by appropriate calculations.

RESULTS

The significant results of this study are given in Table 1, which includes illustrative cases with shift of the electrocardiogram with

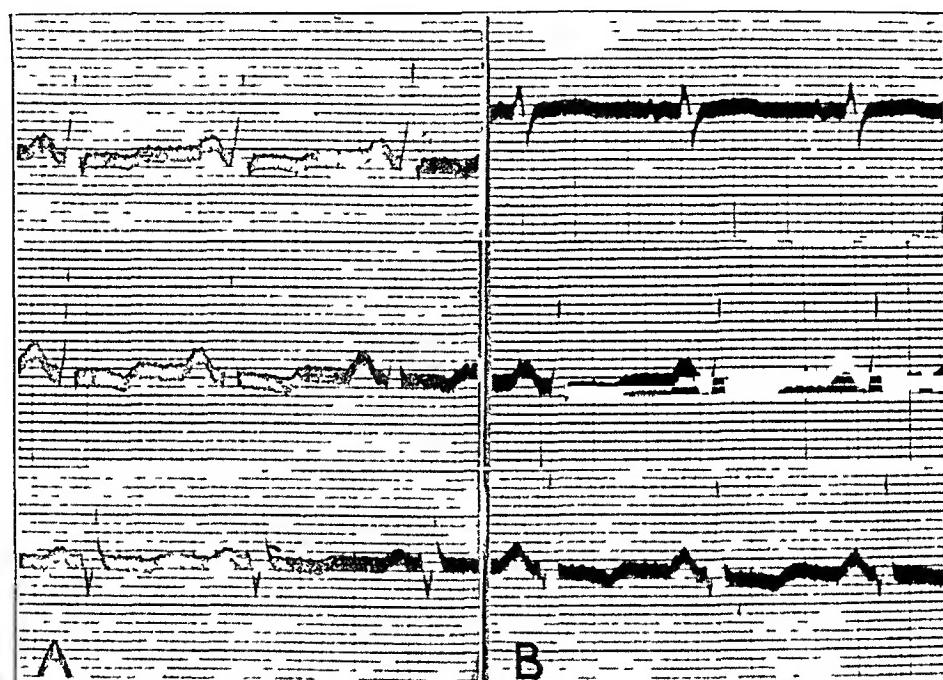


Fig. 2 (Case 3)—*A*, patient on right side; *B*, on left side, marked change in form of Leads I and III.

postmortem examination, and all of the cases, with or without necropsy in which the record showed practically no change. Table 2 summarizes the data of all the observations.

No normal individuals in whom there was not a definite change in the form of the electrocardiographic record on rotation of the body have been encountered, although the change is sometimes not as marked as it is in patients with cardiac disease. In a series of fifty observations on patients with heart disease, four instances in which the record showed practically no shift were seen, and seven in which there was only a very slight shift. Thirty-three patients, including all those whose electro-

TABLE 1—*Data of Illustrative Cases with Shift of the Electrocardiogram on Change of Position and All Cases with Insignificant Shift*

Case	Age	Type of Heart Disease	Clinical Signs of "Adhesive Pericarditis"	Electrocardiogram	Necropsy
1	39	Rheumatic	Apex fixed, systolic apical retraction	Marked shift Figure 1	Pericardium, no lesion, mediastinum, no lesion, weight of heart, 740 gm
2	48	Sclerotic coronary occlusion	Apex fixed	Marked shift Figure 1	Pericardium no lesion mediastinum, no lesion, weight of heart, 520 gm
3	37	Hypertensive (septicemia Streptococcus hemolyticus)	Apex fixed	Marked shift Figure 2	Pericardium and pericardium densely adherent, mediastinum, no lesion, weight of heart and pericardium, 1,240 gm
4	19	Rheumatic	Apex fixed, systolic apical retraction	Marked shift Figure 3	Pericardium, no lesion, mediastinum, no lesion, weight of heart, 600 gm
5	38	Syphilitic	(1) (Pericardial rub) (2) Apex fixed, Broadbent's sign	(1) Slight shift (2) No shift, Figure 4	Pericardium and pericardium densely adherent, many adhesions between mediastinum and pericardium weight of heart, 980 gm
6	21	Rheumatic	(Pericardial rub), apex fixed	No shift Figure 5	Pericardial cavity obliterated, dense pleuropericardial adhesions, weight of heart, 1,050 gm
7	21	Rheumatic	(Pericardial rub), apex fixed, systolic apical retraction	Slight shift Figure 6	Pericardial cavity obliterated, delicate pleuropericardial adhesions, weight of heart, 800 gm
8	36	Syphilitic	Apex fixed, systolic apical retraction, diastolic shock	Slight shift	Moderate adhesions between pleuridium and pericardium, many pleuropericardial adhesions, weight of heart, 850 gm
9	43	Nephritis	(Pericardial rub), apex fixed, systolic apical retraction	No shift	
10	22	Rheumatic	Apex fixed, systolic apical retraction, Broadbent's sign	Slight shift	
11	16	Rheumatic	Apex fixed, Broadbent's sign	Slight shift	
12	23	Syphilitic, tuberculous	Apex fixed	Slight shift	
13	22	Tuberculous	(Pericardial rub), apex fixed, diastolic shock	Slight shift	
14	15	Rheumatic	Apex fixed, (pericardial rub?)	Slight shift	
15	44	Rheumatic?	(1) (Pericardial rub) (2) Apex fixed, systolic apical retraction	(1) Marked shift (2) No shift	

(1) Early admission (2) First admission

TABLE 2—*Summary of Results*

Total observations	50
Cases with signs of "adherent pericardium"	33
No shift of electrocardiogram (all with clinical signs)	4
Necropsies (Both showing dense adhesions of pericardial cavity and mediastinum)	2
Very slight shift of electrocardiogram (all with clinical signs)	7
Necropsies (Both with moderate involvement of pericardium and mediastinum)	2
Marked shift of electrocardiogram (all with clinical signs)	22
Necropsies (None with combined pericardial and mediastinal lesions)	5

cardiogram did not change significantly, had some indication of signs which are frequently associated with "adherent pericardium." Twelve patients came to necropsy, including eight with signs suggestive of the lesion and, among these eight, four patients whose electrical axis remained relatively constant. All four of these individuals with fixed electrical axes had important lesions of the pericardium and of the mediastinum which were present in none of the other patients on whom postmortem examinations were done.

In Case 3, although the pericardial cavity was practically obliterated, there were no lesions of the mediastinum. In Case 4, there were a

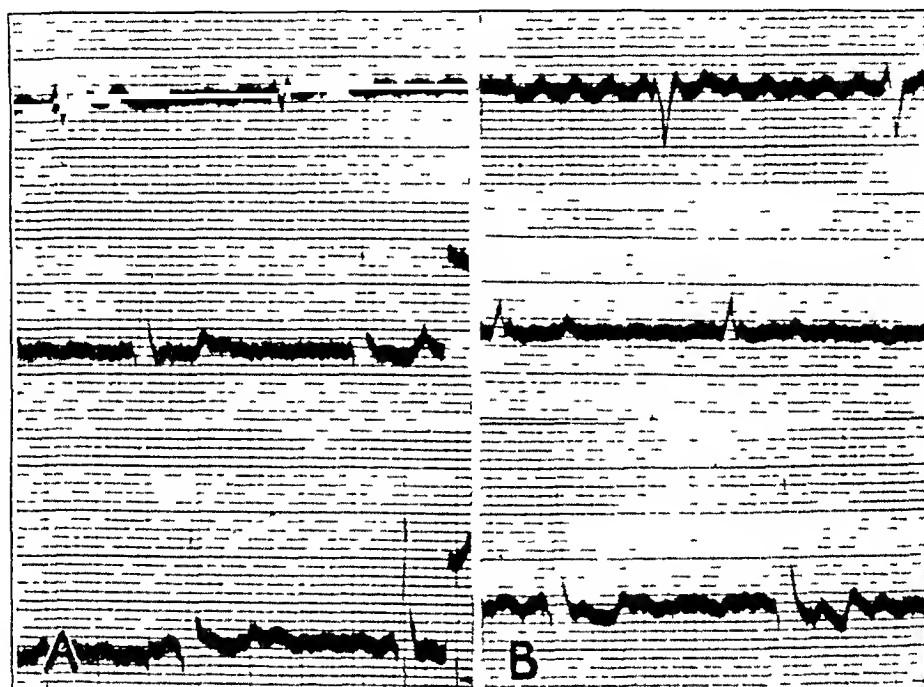


Fig. 3 (Case 4).—*A*, patient on right side, *B*, on left side, marked change in Leads I and II.

few delicate adhesions between the mediastinum and the pericardium, but none within the pericardium. The records of both these patients changed markedly with the rotation of the individuals. In Cases 7 and 8, the lesions of the mediastinum were not marked, and the electrocardiograms shifted slightly.

It is noteworthy that the series includes several patients with marked enlargement of the heart (in one case the heart weighed 860 gm.), whose records showed the usual shift (Figs. 1, 2 and 3).

Of especial interest, at least potentially, is the case of the patient (Case 15) who when first seen had an attack of acute pericarditis, at which time the electrocardiogram changed with the change in position

Two months later, there were suggestive clinical signs of adhesive pericardial mediastinitis, and the record remained constant. This patient is still under observation.

COMMENT

Of the difficulty of making the diagnosis of adhesive pericardial mediastinitis, little need be said. It has long been recognized that adhesions between the two pericardial layers, although they may lead

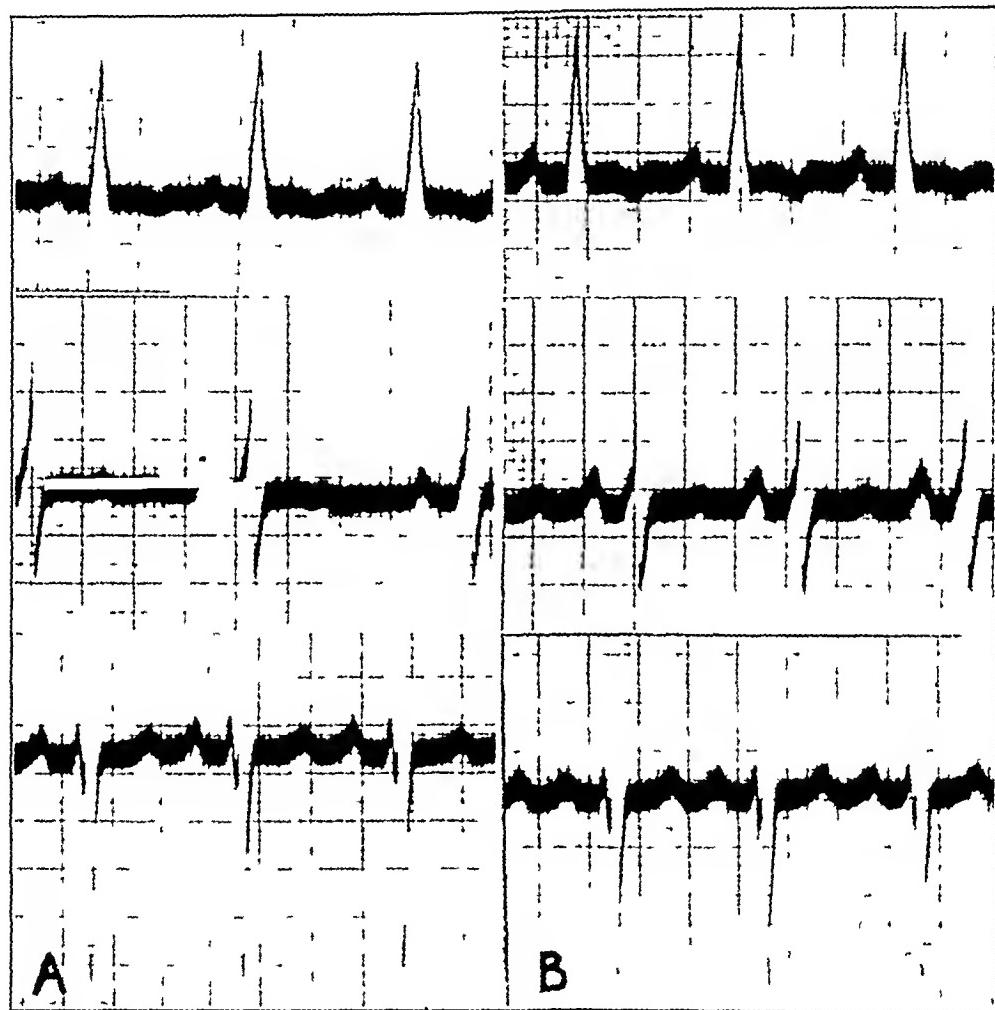


Fig. 4 (Case 5)—*A*, patient on right side, *B*, on left side, no change with shift in position.

to embarrassment of the heart, can hardly be diagnosed clinically. On the other hand, mediastinitis, perhaps as a rule, does not involve the heart at all. Therefore, the condition which we may hope to diagnose clinically, and which is of great importance from the cardiac standpoint, is a combination of chronic adhesive pericarditis, properly speaking, and mediastinitis. This may be termed chronic adhesive pericardial mediastinitis. It is to this condition that the sign here reported, if it is confirmed, has reference.

The normal change in the electrocardiogram is, of course, undoubtedly due to movement of the heart and the consequent bringing into the record of potential differences in planes which are not recorded in the usual position. That it is not due entirely to lateral movement is shown by the fact that it may occur when the apex is fixed, and also by the fact that changes in the position of the heart produced by pneumothorax or pleural effusion have only a small influence on the form of the record. (It is to be remembered that the effect in the cases

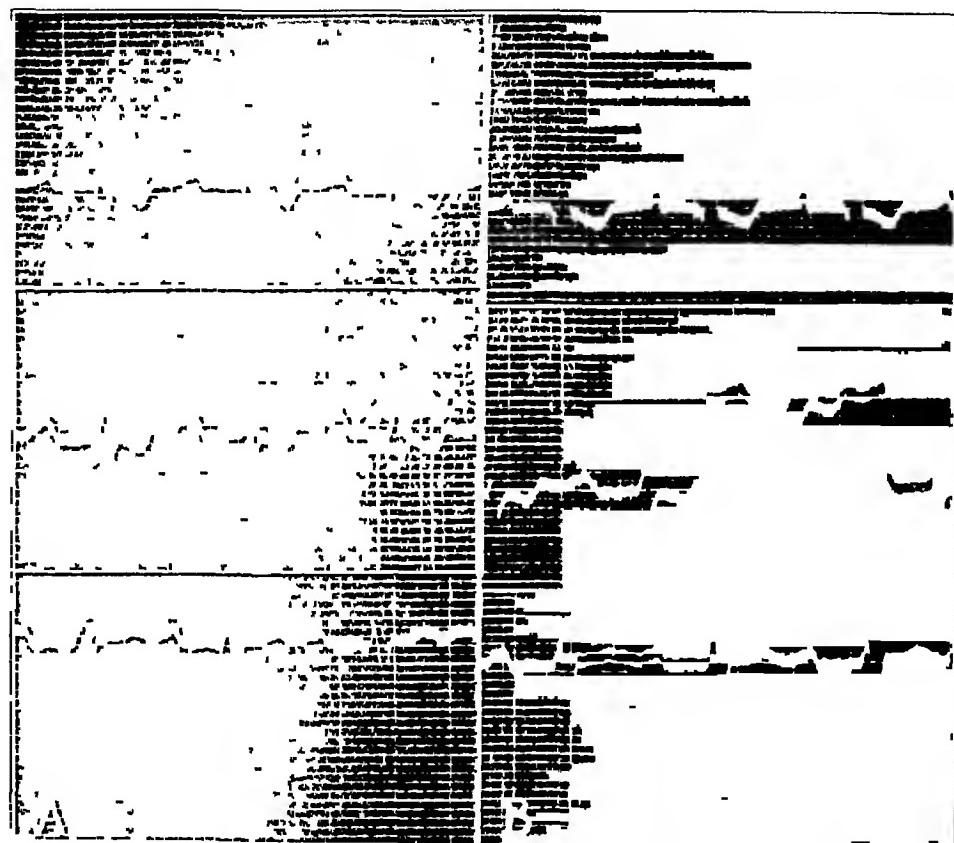


Fig 5 (Case 6)—*A*, patient on right side, *B*, on left side, no change with shift in position

of true dextrocardia is due to reversal of the chambers of the heart, together with the branches of the bundle of His.) The change is, therefore, due to rotation of the heart about a longitudinal axis. It might be expected to disappear when the heart is fixed, since there can then be no change in the relation of the plane from which the potential differences are recorded and the ultimate leading off points, which are, of course, not the extremities.

In some instances, the interpretation of the records secured is difficult. This is not infrequently the case in the presence of auricular

fibillation, owing to intrinsic variation in the amplitude of all of the waves. Figure 3 shows, however, that the shift may be readily seen in some cases. In the absence of auricular fibrillation, the same phenomenon may rarely cause difficulty. In one case, we have obtained within a short time of each other records showing a moderate change and practical fixation of the electrical axis. No satisfactory explanation can be offered for this, although, on the basis of the clinical evidence, the impression is that fixation of the heart is in progress.

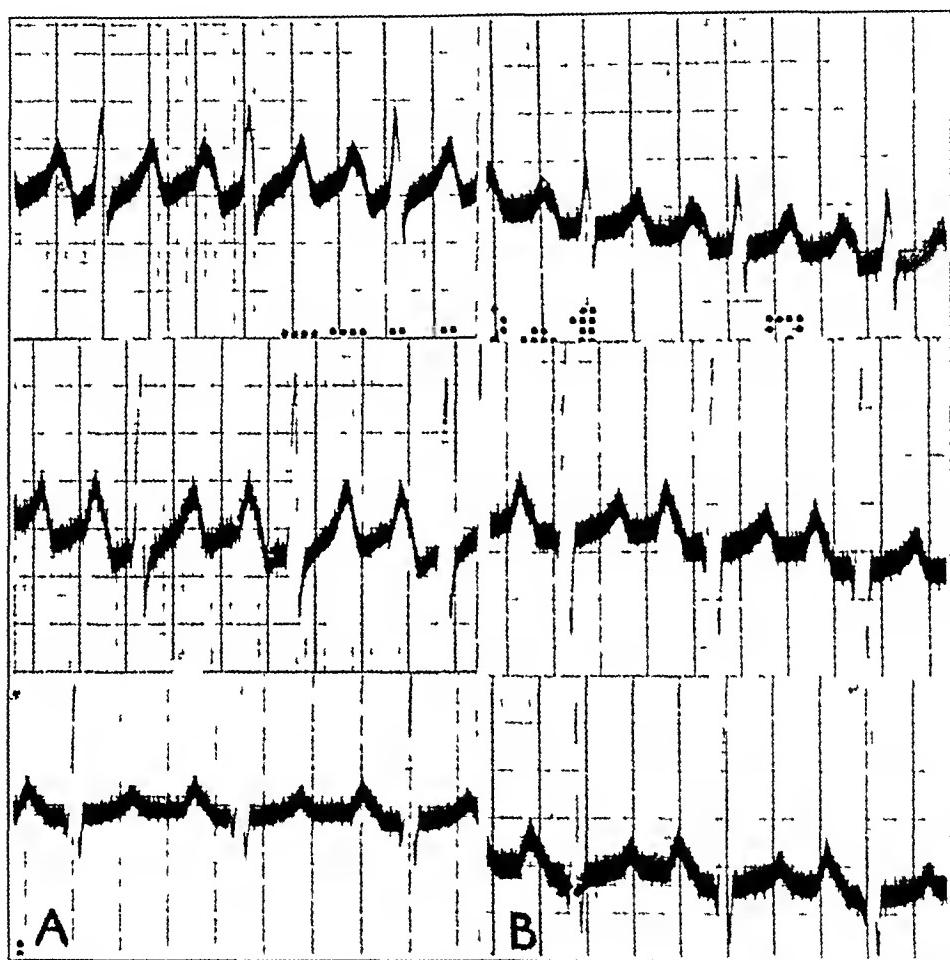


Fig. 6 (Case 7).—*A*, patient on right side; *B*, on left side, slight change with shift in position.

The evidence available does not warrant an attempt to estimate partial fixation of the heart, nor should this be done without suitable anatomic control.

Theoretically, the phenomenon reported may be expected to occur. The number of cases available for complete study has been small and is, perhaps, not conclusive evidence. It is significant, however, that failure of the electrocardiogram to change with the shift in the position of the subject is unusual and apparently of no greater frequency than

fixation of the heart as a postmortem finding. It is hoped that evidence may be accumulated, and it is suggested that patients with acute pericarditis who may later develop the chronic lesions, as well as those suspected of having chronic adhesive pericardial mediastinitis, be studied in the manner described.

SUMMARY

1 Normally there is a change in the form and amplitude of the electrocardiographic waves on shifting the subject from the right to the left side. This phenomenon is marked in most patients with heart disease. It is due to rotation of the heart.

2 It is shown that cardiac enlargement does not prevent the usual change.

3 Clinically, we may only hope to diagnose instances of "adherent pericardium" in which both the pericardial cavity and the mediastinum are involved by adhesions.

4 A small series of patients is reported who showed no significant change in their electrocardiographic record with a shift in position. All of these who came to necropsy were found to have important lesions involving both the pericardium and the mediastinum. Of a larger series of patients with clinical signs of "adherent pericardium," whose records showed a marked change, none were found to have lesions both of the pericardium and of the mediastinum.

5 It is suggested that fixation of the electrical axis, determined by this means, may serve as objective evidence of this lesion.

THE RESPIRATORY GAS PERCENTAGES DURING NITROUS OXID ANESTHESIA IN DOGS*

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AND
HIRAM M CURREY, A.M
COLUMBIA, MO

The practical induction of nitrous oxid-oxygen anesthesia by the methods now universally practiced still leaves undetermined the question of adequacy of the supply of oxygen to the patient

The question as to availability of oxygen is rendered the more important by recent work which tends to establish the minimum requirements of oxygen in respiratory airs for efficiency in the normal individual. The experimental data of the United States Army School of Aviation Medicine prove that a normal man cannot long retain consciousness unless he breathes air of at least 6 per cent oxygen¹. In the tests, it is assumed that the individual is exerting a minimum of muscular activity. He is not far from the normal basal metabolic level. By the least additional work, as by any sudden muscular acts, he quickly consumes the oxygen below the level necessary to retain consciousness. For less resistant individuals, either normal or pathologic, a greater percentage of oxygen must be supplied. This critical oxygen level in the Air Service tests is not far different from that of the oxygen percentages in nitrous oxid-oxygen mixtures during practical anesthesia.

Working with dogs, we have undertaken to study the percentage of the gas mixtures which these animals must breathe to induce a surgical stage of anesthesia, namely, complete muscular relaxation and the regular respirations and circulatory conditions characteristic of an even stage of anesthesia.

REVIEW OF LITERATURE

Not much has been done in the analysis of the respiratory gases during prolonged nitrous oxid-oxygen anesthesia. Kemp,² in 1896,

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* The data of this paper were presented in a thesis by the junior author in partial fulfilment of the requirements for the degree of Master of Arts in the University of Missouri.

* We are indebted to the Committee on Therapeutic Research of the American Medical Association for aid in the purchase of necessary apparatus.

¹ The literature on anoxemia is listed by Schneider, E. C., and Truesdell, Dorothy Am J Physiol 55 223 (March) 1921, and by Greene, C. W., and Gilbert, N. C. Am J Physiol 60 155 (March) 1922

² Kemp, G. T. Nitrous Oxid Anesthesia, Brit M J 2 1480, 1897

supplied his experimental dogs with nitrous oxid and air, the percentages not given, and made five experiments with 10, 61, 65 and 115 per cent oxygen in the mixtures breathed. It is not clear from his data what stage of anesthesia was reached, especially in the experiments with the higher percentages of oxygen with nitrous oxid.

Cullen, Austin, Kornblum and Robinson³ published the results of two experiments in which they state that "it was found impossible to secure anesthesia in the dog without using 95 per cent or more of nitrous oxid. This inevitably led to marked anoxemia." These observations were made in their study of the initial acidosis in anesthesia. They used pure oxygen, 5 parts, with nitrous oxid, 95 parts. They also tested anoxemia by administering nitrogen followed by a mixture of 95 parts nitrogen and 5 parts oxygen.

Leake and Hertzman,⁴ in studies on blood reaction in ethylene and nitrous oxid anesthesia, administered nitrous oxid and oxygen to dogs using 85, 90 and 95 per cent by volume of nitrous oxid with pure oxygen in their inhalant mixtures. They state "Under nitrous oxid and oxygen, it is impossible to obtain true anesthesia without some degree of anoxemia."

EXPERIMENTAL METHODS

In the present experiments, normal dogs were anesthetized through a face mask. They were given pure nitrous oxid for a certain number of respirations in order to remove the excess of pulmonary and tissue nitrogen, then switched to a predetermined mixture of nitrous oxid and oxygen. The mixture was conducted to the face mask through one-way flutter valves. The mixing was obtained in a large gasometer, and by a McKesson nitrous oxid-oxygen apparatus. The exhalant tube was so controlled as to discharge into a rebreather, into outside air, or into a Tissot apparatus, thus enabling one to examine the exhaled as well as the inhaled gases.

Dogs vary in their susceptibility to nitrous oxid in oxygen mixtures. Broadly speaking, by this technic it requires a reduction to 6 and sometimes to 5 per cent of oxygen in the inhaled gas to induce and maintain anesthesia. Very slight variations from the necessary concentration for the particular animal would either induce light anesthesia or stop respirations, according to the direction of the change in mixture. The narrow working margin was always a surprise.

³ Cullen, G. E., Austin, J. H., Kornblum, K., and Robinson, H. W. The Initial Acidosis in Anesthesia, *J. Biol. Chem.* **56** 679 (June) 1923.

⁴ Leake, C. D., and Hertzman, A. B. Blood Reaction in Ethylene and Nitrous Oxid Anesthesia, *J. A. M. A.* **82** 1162 (April 12) 1924.

Gas samples were taken from this apparatus through three channels (1) from the inhalant tube between the McKesson mixer and the respiratory valves, (2) from the exhalant tube outside the valve system, (3) in a certain number of experiments, deep alveolar gas samples were taken. From analyses of the first, the accuracy of the mixture inhaled was confirmed, and from the other samples the various data as to respiratory oxygen availability and carbon dioxide output were obtained.

GAS ANALYSIS METHODS

The Haldane air analysis apparatus was used for gas analysis, the principal steps in the analysis being, first, the absorption of carbon dioxide by caustic potash, second, the absorption of oxygen by an alkaline pyrogallate solution, and third, the estimation of nitrous oxide by difference. The method of analysis is applicable to nitrous oxide-oxygen-carbon dioxide mixtures without nitrogen, or with known nitrogen. In this series, the samples were taken only after the respiration had proceeded to a point where it could be safely assumed that all the nitrogen or at least all but mere traces had been removed.

Nitrous oxide, like carbon dioxide, is extraordinarily soluble.⁵ Kunerth has shown that nitrous oxide is soluble in water to as much as 44.9 per cent by volume at 36°C. It is sparingly soluble in saturated potassium hydrate solutions and in saturated potassium hydrate-pyrogallate solutions. However, the physical solubility of the gas must be taken into account in determining the total nitrous oxide in a gas sample by this method.

Solubility curves were run on the apparatus used and on mixtures containing known quantities of nitrous oxide and oxygen. From these, a correction factor was obtained for the approximate mixtures found in actual analyses. The percentage of error by this technic is large for physical purposes, but it is insignificant in view of the main question at issue.

EXPERIMENTAL RESULTS

Over fifty experimental gas analyses were made in order to determine the range of oxygen-nitrous oxide mixtures, during effective anesthesia. In the dog, it is difficult to identify comparable states of anesthesia. Deep anesthesia is characterized by complete muscular relaxation. However, loss of voluntary motion occurs much earlier, but muscular clonic contractions may occur up to the onset of deep

⁵ Kunerth, William. The Solubility of Carbon Dioxide and Nitrous Oxide in Certain Solvents, Physical Review 19, 512, 1922.

anesthesia Dogs will give uncoordinated vocalization at a concentration of nitrous oxid within 1 per cent of an effective anesthetic mixture For example, an animal in surgical anesthesia at 6 per cent oxygen and 94 per cent nitrous oxid will soon recover sufficiently from this stage to give uncoordinated vocalization when the percentage of oxygen is raised to 7 with 93 per cent nitrous oxid During experiments, the respiratory movements were recorded by the Sargent's belt stethograph The character of the respiratory tracing furnished a very good supplementary index of the stage of anesthesia

The experiments are set forth in groups, depending somewhat on the development of technic during the work

TABLE 1—*Analysis of Initial Mixture and Residual Gas in Apparatus After Complete Relaxation*

Experiment	Date	Dog	Temper- ature	Initial Rebreather Mixture		At Establishment of Anesthesia		
				Oxygen per Cent	Nitrous Oxid, per Cent	Carbon Dioxide, per Cent	Oxygen, per Cent	Nitrous Oxid, per Cent
1	1/31	1	24	12.81	87.67	0.02	3.5	95.87
2	2/2	1	24	9.82	91.08	0.1	2.28	93.4
3	2/2	2	24	11.75	87.97	0.25	2.17	95.64
4	2/7	2	25	11.64	88.36	0	2.91	97.08
6	2/7	2	25	3.29	96.7	0	3.11	96.89
7	2/7	2	25	4.67	95.33	0.07	3.96	96.01
9	2/9	1	26	4.81	95.17	0.02	4.84	95.16

Nitrous oxid oxygen mixtures were given from a rebreather in which the first few exhalations were wasted to the exterior, then the system closed The gas samples at the close of the experiment were taken from the exhalant tube before carbon dioxide absorption, in Experiments 1 to 3 from the inhalant tube just outside the valves, in Experiments 4 to 9, hence these represent the composition of the gases inhaled and exhaled at the moment anesthesia was established

In Group 1, a large volume of an initial mixture assumed to be adequate for anesthesia was rebreathed by the animal until anesthesia was induced Analyses of the initial mixture and of the residual gas in the apparatus after complete relaxation are presented

In Group 2 the animal also rebreathed a mixture by the closed circuit method But the animal was given a corresponding preliminary gas-oxygen mixture from the McKesson apparatus for a sufficient time to remove the nitrogen from the lungs and system It was then switched to the rebreather filled by the same mixture but checked by analysis The terminal gases were also analyzed, in this group The advantage of the method consists in the fact that the oxygen was progressively but slowly reduced in the mixture, thus enabling one to judge more accurately the partial percentages of nitrous oxid at the different stages of anesthesia as between light, medium and deep

TABLE 2—Second Group Given Preliminary Gas-Oxygen Mixture from McKesson Apparatus

Ex- peri- ment	Date	Dog	Tem- pera- ture	Initial Rebreather Mixture			At Establishment of Anesthesia			
				Nitrous Oxygen, per Cent	Nitrous Oxid, per Cent	Carbon Dioxide, per Cent	Nitrous Oxygen, per Cent	Nitrous Oxid, per Cent	Carbon Dioxide, per Cent	
10	2/ 9	1	24	—	—	0	3 65	96 35	0	Deep
11	2/14	2	24	4 77	95 23	0	3 77	96 23	0	Medium
12	2/14	2	24	7 87	92 13	—	3 82	96 18	—	Medium
13	2/15	2	24	7 61	92 39	0 08	4 19	95 79	0	Light
14	2/15	2	25	—	—	0	4 19	95 79	0	Medium
15	2/16	2	25	4 92	95 08	0	3 88	96 12	0	Deep
17	2/23	2	23	7 62	92 35	0 03	3 62	96 38	0 025	Light (?)
18	2/23	2	24	4 64	95 36	—	3 8	96 2	0	Light (?)
19	2/28	3	24	4 25	95 75	—	4 24	95 75	0 015	Medium
20	2/28	3	24	5 5	94 48	0	4 04	95 96	0	Medium
22	3/ 2	3	24	4 75	95 25	0	4 17	95 85	0	Medium

Nitrous oxid oxygen mixtures were given from a closed rebreather. This set differs from Group 1, Table 1, in the thoroughness of the preliminary washing out of nitrogen from the lungs and tissues by gas mixtures from a McKesson apparatus before connecting with the rebreather mixture.

Group 3 received nitrous oxid-oxygen directly from the McKesson apparatus, wasting the exhaled gases into the external air, with samples into a Tissot apparatus during the anesthesia stages desired. This technic closely imitates the practical methods of gas administration in that the gas mixture can be varied instantly, or the animal can be held for long periods at a definite and constant stage of anesthesia. Respired mixtures were sampled from the inhalant and exhalant tubes outside the controlling valves.

TABLE 3—Third Group in Which Gas Mixtures Were Supplied Directly from McKesson Apparatus

Ex- peri- ment	Date	Dog	Tem- pera- ture	Inhaled Gases			Exhaled Gases			
				Nitrous Oxygen, per Cent	Nitrous Oxid, per Cent	Carbon Dioxide, per Cent	Nitrous Oxygen, per Cent	Nitrous Oxid, per Cent	Carbon Dioxide, per Cent	
23	3/ 7	3	25	21 23	79 75	0 02	—	—	—	—
24	3/ 7	1	24	5 71	94 29	0	—	—	—	—
25	3/ 9	4	23	2 37	97 5	0 13	—	—	—	—
26	3/ 9	4	25	3	97	0	—	—	—	—
27	3/14	4	23	6 86	93 14	0	—	—	—	—
28	3/14	3	26	5 63	94 37	—	—	—	—	Light
29	3/16	4	23	7 48	92 34	0 18	5 93	92 58	1 49	Light
30	3/16	3	23	6 54	93 46	—	5 43	92 75	1 82	Light
31	3/21	3	26	6 72	93 2	0 08	5 21	93 44	1 45	Medium
32	3/23	4	23	5 09	94 91	0	4 38	93 6	2 02	Light
33	3/28	3	24	6 74	93 26	0	—	—	1 37	Light
34	3/28	4	24	11 49	85 51	0	9 41	88 32	2 27	Very light
35	3/30	4	24	6 71	93 29	0	5 44	92 93	1 63	Light
36a	4/ 4	3	22	4 06	95 94	0	3 86	94 93	1 32	Medium
36b	4/ 4	3	23	3 54	96 46	0	—	—	—	—
37	4/ 6	4	23	10 75	85 25	0 12	8 47	89 37	2 16	Light
39	5/ 2	3	24	7 85	92 15	0 08	6 21	91 63	1 86	—
40	5/ 4	3	21	9 04	90 96	0	8 01	89 27	2 11	—
41	5/ 4	3	23	6 18	93 82	0	5 34	95 51	1 44	Light
42	5/ 4	3	26	4 4	95 60	0	2 9	95 24	1 77	Deep
43	5/ 4	3	23	9 6	91 4	0	—	—	—	Light
44	5/ 8	4	22	14 66	85 44	0	11 08	85 44	3 48	Very light
45	5/ 9	5	23	7 64	92 36	0	—	—	—	Light
46	5/ 9	5	24	3 57	96 43	0	—	—	—	—

Samples of inhalant and exhalant gases were simultaneously drawn from outside the corresponding valves at the stage when anesthesia was constant.

In Group 4, chlorbutanol was administered to keep the animal quiet on a chlorbutanol metabolism level. The relation of the inhaled and exhaled gases is shown. But this series was done primarily to cooperate with simultaneous blood gas studies.

In these series, the records of respiratory movements were invaluable as a supplement to direct observations of the animal itself. In the first series, the analytic samples were taken during the more profound stages of anesthesia. The percentage of oxygen, at this time, was unexpectedly low, between 2.17 and 4.84 per cent. The nitrous oxide averaged, therefore, about 95 per cent in these mixtures. Compared with man, the dog is known to be much more resistant to low oxygen. In a long series of experiments on anoxemia, Greene and Gilbert¹ have shown that dogs do not cease breathing until the amount of oxygen available in the air they breathe is reduced to between 3 and 4 per cent. They report one experiment with as low as 1.96 per cent of alveolar

TABLE 4.—Fourth Group in Which Chlorbutanol Was Administered

Experiment	Date	Dog	Temperature	Inhaled Gases			Exhaled Gases		
				Oxygen, per Cent	Nitrous Oxid, per Cent	Carbon Dioxide, per Cent	Oxygen, per Cent	Nitrous Oxid, per Cent	Carbon Dioxide, per Cent
47	5/11	6	24	22.72	77.28	0.02	21.28	77.32	1.4
48	5/11	6	22	20.18	79.82	0	19	79.28	1.72
49	5/11	6	24	7.31	92.66	0	7.7	91.4	0.97
50	5/18	7	20	17.29	82.71	0	11.51	83.09	3.4
51	5/18	7	23	7.83	92.17	0	4.51	91.79	3.74
52	5/18	7	24	17.75	82.25	0	14.32	84.88	4.12
53	5/18	7	24	8.83	91.17	0.16	5.88	90.87	3.25

These data were obtained from chloroformized dogs manipulated as in Group 2, except that rebreather records were taken to determine the rate of oxygen consumption. Simultaneous inhalant and exhalant gases (before carbon dioxide absorption) are presented.

oxygen at the moment respiration stopped. The present nitrous oxide-oxygen series approaches in concentration of nitrous oxide that observed for nitrogen anoxemia in their experiments.

When the inhaled gas from a rebreather is analyzed at the earliest identifiable surgical anesthesia stage, the values for oxygen have been from 4.9 to a minimum of 3.6 per cent, figures somewhat higher than in the first series.

In Group 3, consisting of twenty-one experiments, the nitrous oxide-oxygen mixture was supplied directly from the mechanical mixing valves of the McKesson apparatus. Samples of both inhalant and exhalant mixtures were analyzed, and attempts were made to secure a variety of experimental stages from very light to deep anesthesia. The stages were judged in a large degree by the response to sensory stimulation, by the degree of muscular relaxation, and by the amount of reflex or voluntary control. In the dog, the eye reflexes are of comparatively

little value in determining stages of nitrous oxide narcosis since the eye reflex is retained even in the deepest stages of anesthesia.

In the lightest anesthesias, for example, Experiments 34, 37 and 40, the exhaled gas contained from 8.01 to 9.41 per cent oxygen, an amount considerably above the inhaled percentages of oxygen during very deep anesthesias. These were not relaxed enough to be surgically satisfactory. It is questionable whether they should be classified as true anesthesias. Experiment 44 was even more questionable. In our series, very deep anesthesia was induced only by an inhalant gas mixture of less than 5 per cent by volume of oxygen.

Attempts were made to secure samples of respiratory gases from an animal at successive stages during one experimental gassing. The results may be seen in Experiment 45, for light anesthesia, and Experiment 46, for very deep anesthesia. These two experiments illustrate the fact that the inhalant mixture, for light anesthesia, must contain not more than 7.6 per cent by volume of oxygen, and, for deep anesthesia, as little as 3.49 per cent by volume. The corresponding exhaled gases contained 5.19 and 2.58 per cent by volume. This particular dog was somewhat less resistant to low oxygen than many observed, yet the outstanding facts indicate that in him nitrous oxide-oxygen anesthesia of the surgical stage can be successfully approached only by approximately from 94 to 96 per cent by volume of nitrous oxide in the inhaled mixture. Such experiments lend support to the assertion of Dr. McKesson in his chairman's address before the American Association of Anesthetists at San Francisco, June 6, 1923, that nitrous oxide serves its primary function as a diluent of oxygen during the induction of nitrous oxide-oxygen anesthesia. So low a percentage of oxygen in inhaled airs inevitably induces a degree of anoxemia.

Throughout the progress of these experiments on dogs, there were general facts of outstanding import which occurred over and over again. Most important of all was the quick response of the animal to the slightest variations in the percentage mixture of nitrous oxide and oxygen from the anesthesia mixture. If the proportion of nitrous oxide was reduced only 1, or at most 2, per cent, dogs would recover within a few minutes; if increased, respirations would quickly slow down and stop. If respirations ceased, however, a single artificial respiration of pure air would usually suffice to restore the animal to normal breathing. In other series of experiments in which blood pressure was measured during nitrous oxide anesthesia, it was determined that the circulation was strong and vigorous at the time respirations ceased, a fact which coincides with the condition of the circulation in extreme anoxemia.

SUMMARY

1 Dogs, anesthetized by adequate mixtures of nitrous oxid and oxygen, pass through stages of analgesia, loss of reflexes and muscular relaxation. These stages cannot be produced by nitrous oxid except in the presence of a proportionate reduction of oxygen, ranging from a maximum of 11.5 per cent down to a lower limit of 3.6 per cent by volume. The higher oxygen percentages will not induce satisfactory surgical anesthesia in dogs.

2 During light and borderline anesthesia, the amount of oxygen in nitrous oxid-oxygen mixtures exhaled by the dog may be from 8.01 to 9.41 per cent, but averages lower, from 4.38 to 5.93 per cent, in medium anesthesias, from 3.88 to 5.20 per cent by volume. The lower figure induces profound relaxation.

3 Analyses of exhaled nitrous oxid-oxygen mixtures indicate that a residuum of from 3 to 4 per cent by volume of oxygen is adequate to support the basal physiologic processes.

4 Complete and rapid recovery from nitrous oxid-oxygen anesthesia takes place in the dog within from thirty seconds to three minutes from the time the animal begins breathing atmospheric air.

5 Dogs will stand repeated administrations of nitrous oxid-oxygen through a period of months with no apparent ill effects to the animal.

THE DISTRIBUTION OF NITROUS OXID AND OXYGEN
IN THE BLOOD OF DOGS DURING
GAS ANESTHESIA *

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Nitrous oxid was discovered by Priestley¹ in 1774, and its anesthetic properties by Sir Humphrey Davy² in 1800. The first attempt to measure the amount of the gas in dog's blood during anesthesia was made by Jolyet and Blanche³ in 1873, a full century after Priestley's discovery. Oliver and Garrett,⁴ 1893, were the first to analyze all the gases of the blood of the dog, comparing the gas distribution before and during nitrous oxid anesthesia. Unfortunately, their results are subject to serious question, and have not been fully confirmed. In the meantime, thousands of nitrous oxid gas anesthesias were performed, and a large body of symptomatic data was developed before the determination of the scientific physiochemical facts on which their explanation rests. The delay was due in no small measure to the difficulties of method.

The ingenious and very workable micro-apparatus of Van Slyke,⁵ 1914, for blood gas analysis has opened anew the field of blood gas studies, because of its far-reaching scientific and clinical applicability. Van Slyke and his collaborators have already published classic contributions. We have sought to apply the methods to a more detailed study of the facts of nitrous oxid distribution in the blood. The practice of mixing oxygen with the nitrous oxid to prolong anesthesia, and the ever increasing physiology of anoxemia both emphasize the vital importance of the availability of oxygen during gas anesthesia. These are the considerations which have inspired the development of the present work.

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* We are indebted to the Committee on Therapeutic Research of the American Medical Association for aid in the purchase of necessary apparatus.

1 Priestley, Joseph Experiments and Observations on Different Kinds of Air, Memoirs of Joseph Priestley to the Year 1795, 1803

2 Davy, Humphrey Research, Chemical and Philosophical, Chiefly Concerning Nitrous Oxid, London, 1800

3 Jolyet and Blanche Compt rend de biol, June, 1873, p 223

4 Oliver and Garrett Lancet 2 625, 1893

5 Van Slyke, D D J Biol Chem 30 347 (June) 1917

HISTORY

The history of nitrous oxid is brought up to the time that is of most importance to this paper by the four recorded dates of our introductory paragraph. To Andrews⁶ of Chicago belongs the honor of adding oxygen to nitrous oxid to render it nonasphyxial. This was an epoch making step. It has proved to be the first practical act in refutation of the prevalent idea of Davy that the body could in some way split off and utilize the oxygen of the nitrous oxid molecule. Andrews made no analyses but rested his practice on the clinical evidence of improvement on adding free oxygen, a step for which, as Gwathmey rightly states, he scarcely received adequate credit at the time.

Bert,⁷ 1878, also added oxygen to nitrous oxid and, in addition, put his patients under an increased pressure in a pneumatic chamber. Bert used this method to confirm argument in favor of the positive anesthetic property of the gas. From 80 to 85 per cent nitrous oxid with from 15 to 20 per cent oxygen under from 5 to 6 atmospheres

TABLE 1—*Gases of Dog's Blood, Per Cent by Volume (Oliver and Garrett)*

	Before Inhalation	After Inhalation
Oxygen	22	349
Carbon dioxide	343	1566
Nitrogen	18	1123
Nitrous oxid		2249

of pressure anesthetized the patient, while the physician outside the chamber, with the corresponding percentages of nitrogen and oxygen of atmospheric air, was of course quite normal. The great solubility of nitrous oxid in the body tissues was not known, and not emphasized as a possible source of displacing oxygen until Hermann⁸ called attention to it in support of the asphyxiation theory, in 1860.

The first effective attempt to determine the amount of gases soluble in the blood during anesthesia was made by Oliver and Garrett,⁴ in 1893. They analyzed the blood of the dog. Their analyses are so significant that the figures are requoted in Table 1.

It is noteworthy that these authors found 18 per cent by volume of nitrogen in normal dog's blood, a figure that was exactly confirmed by the far more carefully guarded determinations of Van Slyke. The excess of nitrogen which they found after gas inhalation was taken as an index of the amount of oxygen made available, following Davy's theory of dissociation. But it is now known that their 18 per cent by

6 Andrews, E J Brit Dent Soc 22, 1869

7 Bert, Paul Compt rend Acad d sc 287, 728, 1878

8 Hermann Brit M J, 1868, p 378

volume before anesthesia represents the saturation of arterial blood by nitrogen under the partial pressures in atmospheric air. Evidently, so great an amount as 11.23 per cent of nitrogen, reported by Oliver and Garrett after nitrous oxid inhalation, represents an impossible supersaturation. The figures can only be interpreted as due to an error from some source not revealed.

Kemp⁹ restudied the gases of dogs' blood to determine by actual measurements the old question of asphyxial (Hermann) versus anesthetic (Davy, Bert) properties of nitrous oxid. Kemp, like Bert, compared nitrous oxid-oxygen mixtures with corresponding nitrogen-oxygen mixtures, but he did not vary the barometric pressures as did Bert. Kemp used the cumbrous Happle methods, fraught with the usual difficulties of extracting large samples of blood. His results in twelve experiments are briefly: Nitrous oxid of the blood varied from 6.9 to 33.5 per cent by volume. There were only two determinations below 20 and more than half were above 28 per cent by volume. Nitrogen averaged 0.4 per cent by volume, with a maximum of 1.1 per cent. Oxygen was found to vary between 2.9 and 17.8 per cent by volume. If all experiments are omitted from Kemp's table for which he records explanatory remarks for irregularities, it appears that the oxygen found falls between 7.9 and 14.2 per cent by volume. He did not determine the oxygen capacities of his blood samples, hence, the percentage saturation cannot be calculated. It is important that Kemp did not confirm Oliver and Garrett's record of an excess of nitrogen in the blood in nitrous oxid anesthesia.

Nicloux,¹⁰ 1908, in careful analyses of blood, found from 20 to 25 per cent by volume of nitrous oxid during anesthesia, and reported 30 per cent by volume at the onset of death. These figures are more constant and somewhat higher than those of Kemp.

Leake and Hertzman¹¹ have just published studies to determine the course of the p_H during prolonged anesthesia. They find that true anesthesia cannot be obtained without a degree of anoxemia. There is at first an increase followed later by a fall in the p_H , which points toward an uncompensated acidosis. The femoral blood contained an oxygen saturation of from 82.3 to 96.2 per cent by volume, a degree of saturation considerably higher than the averages we have found for deep and surgically relaxed stages of anesthesia.

⁹ Kemp, G T Brit M J 2 1480, 1896 This article has an extensive reference list

¹⁰ Nicloux, M Compt rend Soc de biol 1 450, 1908

¹¹ Leake, C D, and Hertzman, A B Blood Reaction in Ethylene and Nitrous Oxid Anesthesia, J A M A 82 1162 (April 12) 1924

METHODS OF EXPERIMENTING

Dogs were used exclusively for the present series of tests. They were bound or held on a specially constructed holder that conformed to the body when the dog was lying on the side. They were anesthetized with nitrous oxid-oxygen mixtures through a face mask. The mask was guarded by inhalant and exhalant flutter valves. The mixture was made through a McKesson gas-oxygen apparatus, and the gases passed through a fairly long inhalant tube to the face mask. The exhaled gases were carried in a corresponding tube far enough to insure a uniform mixture of exhalant airs for sampling. Both inhalant and exhalant respiratory samples were taken for analysis. The respiratory data for a long series of preliminary tests, Experiments 1 to 30, and for the blood series, Experiments 31 to 53, reported here, are given in the preceding paper by Greene and Currey.¹²

Anesthesia was begun with a definite number of inspirations, usually ten, of pure nitrous oxid, in the attempt to remove promptly all nitrogen from the alveoli of the lungs. It was also hoped that this preliminary breathing of pure nitrous oxid would more quickly eliminate the nitrogen from its solution in the blood and body tissues. The machine was then promptly set to a mixture of gas and oxygen assumed to be efficient for anesthesia in the particular animal. Usually, from three to ten minutes were used in the preliminary stages to establish slowly an even and constant anesthesia.

Samples of respiration gases and of bloods from the femoral artery and, on occasion, the vein were drawn as nearly simultaneously as possible. The actual drawing occurred as quickly after an even anesthesia was established as the vessels could be punctured. The procedure was based on the assumption that an established physical balance as between the partial pressures of the gases in the alveoli and their corresponding solutions in the blood of the pulmonary capillaries is represented in the arterial blood samples. Due to the extraordinary responsiveness of dogs to very slight variations of the percentage of oxygen mixed with the nitrous oxid, one could not always judge with fine distinctions the exact intensity of anesthesia in assumed comparative stages. In what we have called very light anesthesia, there always was some muscular movement, but uncoordinated, and some sensory reflex response. We recognize that such stages might possibly be classified as analgesias. Yet these animals, when allowed to breathe pure air, continue to exhibit unmistakable signs of unconsciousness for from ten to thirty seconds, and often much longer. As a matter of

fact, a more exact definition of the signs and degrees of anesthesia is badly needed among scientific workers in this field

At a signal, the two gas samples and the arterial and venous blood samples were drawn, or the inhalant and exhalant airs and the arterial and venous bloods were drawn, each pair in quick succession. The venous bloods were drawn only in a small proportion of the experiments.

The blood samples were taken through Luer needles, sizes 18 to 20. Arterial punctures of the femoral are easy and sure. When venous samples were called for, it contributed to speed and accuracy if the femoral vein was first exposed by a short cut through the skin and fascias made after the onset of analgesia. The blood was drawn into a Van Slyke and Cullen sampler over sodium oxalate powder and under a layer of liquid petrolatum. A 1 by 3 inch (2.5 by 7.6 cm) specimen tube was found to be more convenient than the longer tubes. The oxalate was dissolved in the blood by gently stirring with a rotary motion in the tube in which the sample was drawn. The analyses were made as quickly as possible, beginning immediately after the blood samples were drawn.

The bloods were analyzed in 2 cc samples in duplicate sets in the Van Slyke blood gas apparatus. The steps in technic are the same as described by Van Slyke and Stadie and slightly modified by Greene and Greene. By this method, the oxygen is absorbed in the apparatus and the nitrous oxid is the residual gas, hence, it is determined by difference. Two sources of error are possible by this procedure. The first depends on the extent to which the nitrogen normally in solution in the blood is thrown off during the time of anesthesia and before sampling the blood. We rely on the preliminary washing out of the lungs by pure nitrous oxid and the later substitution of pure oxygen and nitrous oxid to remove a constant stream of nitrogen from the blood and tissues, until this gas is washed out. We have assumed that this process reduces the nitrogen residue in the blood samples to within the limits of error of determination of the total residues of gas. No correction has, therefore, been made for possible residual nitrogen from this source. If the assumption should be questioned, one must reply that the maximal correction would not exceed a small and unimportant fraction of the nitrogen factor determined by Bohr, Van Slyke and the various investigators of the blood gases in more recent scientific and clinical publications. The saturation of arterial blood does not exceed a maximum of 13 to 18 per cent by volume of nitrogen in the normal blood, but we believe it to be near 0 in our samples. We have, therefore, discarded the view of Oliver and Garrett as untenable. Hence, we have abandoned further attempt to measure the nitrous oxid directly from such small

total samples as are yielded from 2 cc of blood, generally between 0.4 and 0.5 cc or less of gases.

The far more important source of deviation arises from the great solubility of nitrous oxid in blood. The solubility in the alkaline fluids of the Van Slyke apparatus is much less than in water, or in blood alone. Yet, after gas liberation under vacuum, the nitrous oxid will rapidly be taken up in solution if, after release of the vacuum, it is allowed to stand for a few seconds before leveling and reading the gas volume. It is very necessary to trap the fluids under vacuum and to read the gas over mercury only. The untrapped fluid can, with care, be reduced to a minimum of 0.1 to 0.2 cc of liquid over the mercury meniscus. If the gas is read promptly, no appreciable resorption occurs.

TABLE 2.—*Nitrous Oxid and Oxygen Content of Arterial Blood and Two Samples of Venous Blood at Different Stages of Anesthesia in the Dog*

Date	Dog No	Ex-periment No	Arterial Blood,		Venous Blood,		Oxygen Capacity, per Cent by Volume	Oxy-gen Saturation, per Cent	Inhalant Air			Degree of Anesthesia		
			per Cent by Volume		per Cent by Volume				Oxy-gen	Nitrous Oxid, per Cent	Oxy-gen Pres-sure, Mm			
			Oxy-gen	Nitrous Oxid	Oxy-gen	Nitrous Oxid			per Cent	per Cent				
3/21/23	3	31	24	21.7	—	—	18.9	13	6.72	93.2	51.1	Deep		
3/23/23	4	32	4.8	20.6	—	—	27.5	17	5.09	94.9	38.6	Deep		
3/28/23	3	33	2.1	26.6	—	—	—	11	6.74	93.2	51.2	Light		
3/28/23	4	34	12.5	24.1	—	—	28	45	11.49	85.5	87.3	Light		
3/30/23	4	35	17.4	19.5	—	—	—	62	6.71	98.2	50.9	Light		
4/4/23	3	36b	12.5	26	—	—	23.2	52	3.54	96.4	26.9	Medium		
4/6/23	4	37	18.2	19	—	—	30.9	50	10.75	85.2	81.7	Light		
5/2/23	3	39	11.9	24.2	—	—	23	51	7.85	92.1	59.5	Light		
5/4/23	3	40	18.8	24	—	—	27.1	70	9.04	90.9	68.7	Light		
5/4/23	3	41	7.9	26.8	7.7	22.2	—	29	6.18	98.8	46.9	Light		
5/4/23	3	42	8.4	24.3	—	—	23.1	36	4.4	95.6	33.4	Deep		
5/14/23	3	43	15	24.5	12.9	21.9	—	65	9.6	91.4	72.9	Very light		
5/8/23	4	44	20.8	—	—	—	24.7	—	14.6	85.4	111.6	Very light		
5/9/23	5	46	4.7	24.5	—	—	22.3	21	3.57	96.4	27.1	Very deep		

Respiratory movements have been recorded as a means of following the progress of anesthesia. The respiratory record furnishes a graphic history not only of the rate and respiratory amplitude, but also of all struggles, vocalizations and the like. As gassing becomes effective and muscular relaxation and evident anesthesia begins, the respiratory movements settle into a uniform and even rhythm and amplitude. We have come to recognize this as a most reliable index of the stage of surgical anesthesia.

The distribution of blood gases in nitrous oxid-oxygen anesthesia has been determined in twenty or more experiments. Arterial blood was used, but both arterial and venous bloods were determined in a number of experiments. The oxygen capacity also was measured and the percentage of saturation calculated. The present blood gas determinations were made in the same series of experiments used as a basis for reporting the nitrous oxid and oxygen in the respiratory airs during different degrees of anesthesia induced in dogs.¹²

An examination of the data of Table 2 reveals a surprisingly high and constant level of partial saturation of the blood with nitrous oxid during anesthesia. The amount of nitrous oxid gas varies between the extremes of 18.9 and 26.8 per cent by volume, an average of 23.3 per cent for Experiments 31 and 46. There is no close correspondence between the depth of anesthesia and the variation of nitrous oxid in the arterial blood within the surgical limits of very light and deep anesthesias. The very deepest anesthesias reported are Experiments 31 and 32, in which the nitrous oxid percentages by volume in the bloods are well under the average, and in Experiments 42 and 46, which have only a little over the average degree of saturation of nitrous oxid. The solubility of nitrous oxid in water, at 36 C, has been determined, by Kunerth,¹³ as 44.9 per cent by volume at 1 atmosphere of pressure. There is no evidence in the literature to indicate that whole blood will absorb any more gas than will distilled water. Apparently, nitrous oxid goes into physical solution in blood and does not form loose chemical compounds, as does oxygen. We have made preliminary determinations that indicate that whole blood takes up about 45 per cent by volume of nitrous oxid when saturated at 25 C. The blood is therefore somewhat more than half saturated at the average of 23.3 per cent by volume reported in the foregoing. The deviations from the average saturation are not constant, and bear little relation to the exact degree of anesthesia. In general, we have come to regard 20 per cent by volume of nitrous oxid as the minimum present when unconsciousness is induced in the dog. We have found over 26 per cent by volume of nitrous oxid present in only two samples of arterial blood, in Experiment 33 with 26.6 per cent, and in Experiment 41 with 26.8 per cent by volume.

In sharp contrast with the nitrous oxid, we have found that the arterial oxygen present varies through a wide range. The table reveals arterial oxygen present all the way from 2.1 to 18.8 per cent by volume. The first was in a relaxed animal with slower, shallow respirations which were near the point of stopping. If we were to draw analogies from the studies on anoxemia by Greene and Gilbert,¹⁴ we should have to assume that the respiratory center was weakening from lack of oxygen. The higher oxygen volumes are all from the blood of animals in light anesthesia, indeed very light from the surgical point of view. The three dogs on which repeated experiments were made during the months of March, April and May yielded bloods of high oxygen capacity,

13 Kunerth, William. Physical Review **19** 512, 1922.

14 Greene, C W., and Gilbert, N C. Responses of Circulation to Low Oxygen Tension, Arch Int Med **27** 517 (May) 1921, Am J Physiol **60** 155 (March) 1922.

varying between 22.3 in Dog 5 and 30.9 per cent by volume in Dog 4. The oxygen capacity of the arterial blood also varied day by day, due to the irregular time of the experiment with reference to feed, drink, etc. Dog 3, a young and growing Airedale, apparently made a steady increase of hemoglobin from the low oxygen capacity level of 18.9 per cent by volume, March 21, to a maximum of 27 per cent by volume, May 4.

The absolute amount of oxygen found must be checked against the blood capacity in determining the availability of oxygen to the tissues. In fact, the capacity factor also conditions the total amount of oxygen absorbed at the lungs. It is now well known that dogs survive when breathing an air of a much lower partial pressure of oxygen than can be endured by man.¹⁵ The higher hemoglobin content of dog's blood enables the blood to take up a correspondingly greater amount of oxygen at its lower partial pressure. The same physical and chemical factors control oxygen absorption from the nitrous oxid-oxygen mixtures. However, in the tissues, the excess of nitrous oxid may prevent oxygen utilization. The high nitrous oxid solubility in the blood and in the tissues is believed to be a factor influencing the rate of diffusion and therefore the time-quantity availability of oxygen. It is an attractive hypothesis to assume that nitrous oxid lowers the amount of oxygen fixed by hemoglobin at any particular partial pressure of oxygen in a manner comparable to that shown by Barcroft and Camis¹⁵ for carbon dioxide. But this hypothesis has no experimental basis as yet. This question and the solubility of nitrous oxid in the tissues are both under investigation.

There are many factors that contribute to variations in the ratios of oxygen and nitrous oxid gases in the blood, and in the blood in comparison with the inhaled mixture. The chief of these are the volume per minute of the gases breathed and the volume per minute of the circulation of the blood. When the circulation is sluggish, an average stage of medium anesthesia can be attained with a gas mixture containing a higher percentage of oxygen. The low respiratory minute volume operates in the same direction. When these two fall together, the observed percentage of oxygen in the anesthetic mixture is highest of all observed. The converse is, of course, true.

As an illustration, it happens that Experiment 31 yielded the lowest nitrous oxid content, and Experiment 41 the highest nitrous oxid content of the arterial series. The first was anesthesia approaching in depth the stage in which respirations cease. The second was a good, quiet, relaxed state but far from the danger line. In these two tests on the same experimental animal, the analyzed percentage of inhaled nitrous

15 Barcroft, J., and Camis, M. *J. Physiol.* **39** 118, 1909.

oxid and oxygen was essentially the same. It was noticed that this animal varied considerably in its reaction intensities during the long time of its use. It was a young animal, and both respiratory and circulatory mechanisms were unusually responsive.

In Experiments 36 and 39 on the same Airedale, the nitrous oxid-oxygen present in the blood was fairly constant, but the partial pressure of the inhalant oxygen in the latter was much higher. The reactions of the animal in the two experiments apparently varied from another angle, i.e., in the second experiment, a reduced efficiency of oxygen absorption and availability. The first experiment showed a percentage of oxygen saturation of the blood only slightly higher than the second, 53 per cent by volume as compared with 51 per cent by volume. The oxygen saturations are greater than in corresponding stages of simple oxygen asphyxiation. In fact, this percentage of oxygen with nitrogen of ordinary air would not produce unconsciousness in any normal animal.

TABLE 3—*A Succession of Nitrous Oxid Experiments on a Young Airedale*

Date, 1923	Experiment No	Inhalant Nitrous Oxid Oxygen	Exhalant Oxygen, per Cent	Arterial		Blood Oxygen Capacity, per Cent by Volume	Saturation, per Cent
				Nitrous Oxid, per Cent	Oxygen, per Cent		
3/21	31	93.3 6.7	5.21	21.7	2.4	18.9	13
3/28	33	93.3 6.7	6.19	26.6	2.1	—	11
4/4	36 b	95.9 4.1	3.86	26	12.5	23.2	52
5/2	39	92.2 7.8	6.21	24.2	11.9	23	51
5/4	40	91 9.0	8.01	24	18.8	27.1	70
5/4	41	93.8 6.2	5.34	26.8	7.9	—	29
5/4	42	95.6 4.4	2.9	24.3	8.1	23.1	36
5/4	43	90.4 9.6	—	24.5	15	—	65

The primary deduction to be made, however, is that, in experimental procedures, considerable variation in the mixture of oxygen and nitrous oxid must be allowed to produce corresponding stages of anesthesia, if there is a corresponding variation in efficiency of the two great mechanisms of respiration and circulation. This relation is reciprocal.

There also must be adjustment as between the percentage of oxygen in nitrous oxid mixtures made from time to time when an animal continues in surgical anesthesia. This, too, depends not so much on metabolism per se as on the deviations in efficiency of the circulation and of the respiration, because of the duration of the anesthesia. For example, in deep, prolonged anesthesia the respiratory volume and rate both progressively decrease. If no other factor operated, this would throw the animal into a still deeper stage of anesthesia, and would, in the end, endanger respiratory rhythm itself. Similar conditions apparently hold with reference to the circulation, particularly when the amount of oxygen is on the borderline of inadequacy. Under these circumstances, the ordinary cycle of events which occurs in extreme

anoxemia is initiated in nitrous oxid anesthesia. The animal may go to the wall rapidly unless the percentage of oxygen is promptly increased and the animal adequately reoxygenated. In these crises, it is not the percentage of variation of nitrous oxid in the mixture but the availability of oxygen at the moment in the tissues which determines the outcome of the crisis.

In Table 3, we have assembled eight experiments on one young Airedale extending over a period of seven weeks. The degree of anesthesia varied from very light with muscular movements present to very deep surgical anesthesia. This table emphasizes the points we would stress. In the first place, the concentration of nitrous oxid found in the blood is surprisingly uniform. It does not vary directly with the stage of surgical anesthesia, in such slight variations as do occur. Comparing Experiments 41 and 42, the first, with the greater concentration of nitrous oxid, had the less profound anesthesia.

These experiments sharply contrast the relation of oxygen percentages to the stage of anesthesia. With an adequate concentration of nitrous oxid in the blood to induce anesthesia, the stage or depth of anesthesia varies directly with the amount of oxygen present. It follows that the control of anesthesia in all gas anesthetics is by the control of oxygen. The problem of anoxemia is always a factor. However, the amount of oxygen present in arterial blood in the lighter and surgical phases is somewhat higher in nitrous oxid-oxygen anesthesia than during oxygen want induced by diminishing the oxygen partial pressures in atmospheric air to a level that will not sustain consciousness.

THE BLOOD PHOSPHORUS IN CHRONIC MYELOG-
ENOUS LEUKEMIA, ESPECIALLY AS INFLU-
ENCED BY ROENTGEN-RAY THERAPY¹

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An abnormal phosphorus metabolism in leukemia has been recognized for over a quarter of a century, and yet very few observations are recorded in the literature relative to the phosphorus content of the blood in this type of disease Moraczewski² in 1898 called leukemia, rather loosely, a "phosphorus and nitrogen disease" and reported not only an increased urinary excretion of phosphorus and nitrogen, but also an abnormally high phosphorus content of the blood. Though numerous studies since then, such as those of Musser and Edsall² and Knudson and Erdos,³ have clearly demonstrated the excessive output of phosphorus in the urine, there seems to be no report of any systematic investigations of the blood phosphorus in chronic myelogenous leukemia entailing an intensive study of cases over a considerable period of time. This is presumably due to the fact that it is but recently that relatively simple methods have become available for determining the blood phosphorus, while those for determining urinary phosphorus have been satisfactory for some years.

The early investigators of the problem failed to distinguish the types of leukemia and consequently not even their few data can be evaluated satisfactorily. Moreover, inasmuch as nearly all of the reported observations regarding blood phosphorus in myelogenous leukemia have had to do either with the whole blood alone or with the plasma alone, it is still an open question whether there exists in this disease, such as exists in rickets, a true disturbance of the phosphorus metabolism, or whether the high level of blood phosphorus is incidental to the leukocytosis.

The present study was undertaken in an attempt to determine whether the phosphorus content of the blood is merely a function of the leukocytosis, or whether it may not be looked on as a manifestation of some more

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* This paper is No 35 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed (in part) by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1 Moraczewski, W Arch f Path Anat **159** 221, 1898

2 Musser, J H, and Edsall, D L Univ Penn M Bull **18** 174, 1905

3 Knudson, A, and Erdos, T Boston M & S J **176** 503 (April 5) 1917

nearly fundamental phase of the activity of the disease. Bearing in mind also the beneficial influence of radium and roentgen-ray irradiation in myelogenous leukemia, it was hoped that by an investigation of the blood phosphorus changes following such irradiation some light might be thrown on the mechanism by which this type of therapy acts. Accordingly, a study of the total and inorganic phosphorus contents of the whole blood, plasma and corpuscles was made in a series of nineteen cases of chronic myelogenous leukemia in various stages of the disease, before, during and after short wave length roentgen-ray treatment. For the purpose of comparing the influence of irradiation therapy on the blood phosphorus in myelogenous leukemia with its influence on the blood phosphorus in cases showing no important degree of leukocytosis, five cases of carcinoma were studied also. Three had carcinoma of the breast, one of the tongue and one of the stomach.

The means of the phosphorus values of the blood of normal persons, reported in a previous paper,⁴ are submitted here and are in accord with the findings of other workers.

METHODS

Blood from a vein was withdrawn under paraffin oil, 0.1 cc. of a 20 per cent solution of neutral potassium oxalate for each 15 cc. of blood being used as an anticoagulant. After thorough mixing, samples of the whole blood were withdrawn from the container for the determinations of total and inorganic phosphorus and for the estimation of the percentage by volume of corpuscles. The remainder of the blood was centrifugalized for twenty minutes at eighteen hundred revolutions per minute, when the supernatant plasma was removed for analysis of its content of total and of inorganic phosphorus.

The percentage volume of corpuscles was estimated by centrifugalizing for thirty minutes at two thousand revolutions per minute, about 1 cc. of whole blood in a carefully calibrated, graduated tube about 5 mm. in diameter, and then reading the fraction of the total volume of blood made up by the corpuscles. Also, in each case an approximate estimation was made of the fraction of the total volume of corpuscles made up by the white cells and blood platelets.

The total phosphorus in the whole blood and plasma was determined by the method of Bloor⁵ and the inorganic phosphorus by the method of Bell and Doisy.⁶ Having determined the total and inorganic phosphorus contents of the whole blood and plasma and the percentage

4 Buckman, T. E., Minot, G. R., Daland, Geneva, and Weld, M. Blood Phosphorus. Its Relation to Cancer and Anemia, *Arch. Int. Med.* **34** 181 (Aug.) 1924

5 Bloor, W. R. *J. Biol. Chem.* **36** 33 (Oct.) 1918

6 Bell, R. D., and Doisy, E. A. *J. Biol. Chem.* **44** 55 (Oct.) 1920

volume of cells, the phosphorus contents of the cells were calculated from these data. The phosphorus determinations are recorded as milligrams of orthophosphoric acid, H_3PO_4 , per hundred cubic centimeters of whole blood, plasma or cells.

The hemoglobin percentage was determined by means of a standardized Sahl instrument and the values given are expressed in terms of the Haldane scale (18.5 per cent by volume of oxygen combining capacity per hundred per cent hemoglobin). Enumeration of the numbers of corpuscles per cubic millimeters of blood and the differ-

TABLE 1.—*Blood Phosphorus in Normal Persons and in Nonirradiated or Not Recently Irradiated Cases of Chronic Myelogenous Leukemia*

Case	Red Blood Cells in Millions	Hemo globin, per Cent	White Blood Cells in Thousands	Per Cent Imma- ture White Blood Cells	Total Phosphoric Acid in 100 Cc			Inorganic Phosphoric Acid in 100 Cc		
					Whole Blood	Plasma	Cells	Whole Blood	Plasma	Cells
Mean value five healthy adults										
1*	4.8	96	8.2		119.3	29.6	233.2	11.0	10.4	12.3
1*	3.5	85	14.6	2	136.6	44.9	342.0	13.5	14.5	11.3
2*	6.4	93	29.9	10	101.9	21.6	194.4	24.3	16.0	34.0
3*	3.9	91	50.0	21	90.2	24.2	191.5	9.8	8.1	12.5
4	4.4	90	78.6	6				14.3		
5*	2.6	47	103.0	14	60.2	34.2	139.0	13.2	11.7	17.7
6*	4.7	75	119.2	28	146.5	18.4	316.0	11.1	11.4	10.8
7*	3.6	81	134.4	41	212.5	27.1	506.1	20.1	12.9	31.6
8*	4.5	65	181.6	49	121.0	43.4	254.0	29.6	16.6	52.2
9*	3.4	59	190.0	20				14.7	11.2	22.1
10	3.9	74	192.0	32	129.9	26.0	348.5	22.3	14.0	39.6
11	2.4	56	216.0	41				14.9	11.6	19.6
12	3.0	54	230.4	18				13.6	9.1	22.2
13	4.1	65	270.0	28	155.7	22.0	318.0	31.5	16.8	47.2
14	3.3	58	281.0	55	236.4	32.7	514.4	31.6	11.5	59.3
15	3.0	47	312.0	46				9.5	7.2	12.6
16	3.5	68	326.0	36	128.2	20.3	283.0	23.1	12.0	39.0
17	3.3	60	353.0	32	245.2	39.8	463.0	30.2	14.5	46.8
18	2.6	50	466.0	75	365.9	20.5	852.0	18.5	3.6	39.4
19	3.3	60	434.0	42	247.5	63.0	460.0	19.1	10.3	32.8
Mean value										
	3.6	68	206.3		169.8	31.2	370.4	19.2	11.8	30.5

* Treated by irradiation, but at a time sufficiently remote from the present observations (i.e., two months or more) to preclude the influence of such treatment, per se, on the phosphorus metabolism.

tial counts of at least 200 white corpuscles in each instance were made in the usual manner. All myeloid white cells less mature than metamyelocytes were classified together as "immature white cells."

OBSERVATIONS

1 *The Findings in Nonirradiated and Not Recently Irradiated Cases of Chronic Myelogenous Leukemia*.—In Table 1 are recorded the results obtained in nineteen cases of chronic myelogenous leukemia. Those designated by an asterisk had received irradiation treatment, but at a time sufficiently remote (over two months) from these observations to preclude any influence of irradiation, per se, on the phosphorus metabolism. The other cases had received no irradiation treatment.

It is evident from inspection of this table that although the levels of total and inorganic phosphorus in the whole blood in the cases of leukemia are generally very much elevated above the mean normal values, the plasma shows no such increase in its content of phosphorus. The mean values for total and inorganic phosphorus in the whole blood of the cases of leukemia are 169.8 mg and 19.2 mg per hundred cubic centimeters of blood, respectively, as contrasted with the mean normal values of 119.3 mg and 11.0 mg. On the other hand, the mean values for total and inorganic phosphorus of the plasma from the leukemia cases are 31.2 mg and 11.8 mg per hundred cubic centimeters of plasma, respectively, as contrasted with mean normal values of 29.6 mg and 10.4 mg. In other words, the increased phosphorus content of the whole blood in chronic myelogenous leukemia is due almost entirely to the increased phosphorus content of the corpuscles.

It is true that in cases of leukemia greater variations occur than in normal persons in the plasma contents of both the total and inorganic phosphorus, and that occasionally very high values are observed 163 mg of total phosphorus per hundred cubic centimeters of plasma in Case 19, and 16.8 mg of inorganic phosphorus per hundred cubic centimeters of plasma in Case 13. These variations in the total and inorganic phosphorus contents of the plasma apparently bear no relation to one another, nor to the phosphorus content of the corpuscles, nor to any of the factors discussed later which are associated with the increase of the corpuscular phosphorus. It could be supposed that the excessive demand for phosphorus caused by the rapid cell proliferation might lead to a paucity of phosphorus in the plasma as suggested by Case 18, in which the total phosphorus content of the blood rose to the very high value of 366 mg per hundred cubic centimeters of whole blood and the total phosphorus content of the plasma dropped to 20.5 mg per hundred cubic centimeters. But this conception is not borne out by the findings in the other cases. On the contrary, the idea might be entertained that enrichment of the plasma in phosphorus should occur as a result of the abnormally rapid disintegration of the cells in the peripheral blood or, teleologically, from the increased demand for phosphorus on the part of the bone marrow. Yet the figures attest that neither of these conceptions is tenable.

The phosphorus metabolism in myelogenous leukemia does not seem to be implicated in the sense that it is in such disorders as rickets, fracture, and certain types of arthritis. If it is, the transport of phosphorus must be effected by the corpuscles themselves, or else in leukemia the equilibrium is maintained carefully between the withdrawal of phosphorus from the plasma by the blood forming tissue, and, the return thereto from disintegrated cells and the subsequent elimination therefrom by the kidneys. Under the conditions of the

observations reported, the plasma phosphorus content in nonirradiated or not recently irradiated cases of chronic myelogenous leukemia is independent of the phosphorus contained in the corpuscles.

More interesting variations are found in the values for corpuscular phosphorus. The phosphorus content of the corpuscles might be and apparently is influenced by several factors among which are (1) the volume of blood platelets, (2) the volume of adult and of immature red blood corpuscles of different types and the percentage of hemoglobin, and (3) the volume of the mature and of the different forms of immature white cells.

It has been shown⁷ that the platelets contain a relatively large amount of phosphorus. As the number of these elements is often increased and sometimes markedly so in chronic myelogenous leukemia, it is reasonable to suppose that when such is the case the elevation of the phosphorus content of the whole mass of cells may be due, in part, to an increase in the volume of these corpuscles. However, it is impossible to determine to what extent this factor is operative for no suitable method exists for the quantitative separation of the total mass of platelets from the other corpuscles. Again, and for the same reason, the fraction of the total phosphorus content of all the cells contributed by the red blood corpuscles can be apprehended only approximately. There is, moreover, another difficulty and that is the presence of large numbers of immature red blood cells in many cases of myelogenous leukemia and these undoubtedly contain more phosphorus than do adult red cells. Thus we have observed the total phosphorus at least as high as 374 mg. per hundred cubic centimeters of red cells in a case of myelogenous leukemia with many immature red corpuscles, and a value for total phosphorus as high as 560 mg. per hundred cubic centimeters of red cells in a case of chronic hemolytic jaundice showing 30 per cent of the red cells to be reticulocytes.⁴ Commensurately high values also have been observed by us in cases of anemia due to blood loss, in which there was an increase in the number of young red cells.

Finally, the same difficulties which are met with in considering the phosphorus content of the platelets or of the red corpuscles recur in considering that of the white cells. The volume of total white cells made up by immature white cells is indeterminate, and even though quantitative separation of the leukocyte fraction of the corpuscles were possible, the methods available for the analysis of such a mass of leukocytes for its content of phosphorus are not satisfactory.

Nevertheless, from a purely statistical consideration of the data, there is an apparently definite relationship between the total phosphorus

⁷ Mathews, A. P. *Physiological Chemistry*, Ed. 3, New York, William Wood & Co., 1920, p. 467. Hammarsten, O. *Physiological Chemistry*, Trans. by Mandel, Ed. 6, New York, John Wiley & Sons, 1911, p. 295.

content of the entire cell volume and the percentage of what have been termed immature white cells. The greater the number of immature white cells, the greater becomes the total phosphorus content of the whole mass of corpuscles. This relationship is illustrated in Chart 1 which shows, also, a similar but less striking relationship between the inorganic phosphorus content of the corpuscles and the percentage of immature leukocytes. The data also show that an analogous but distinctly less definite relationship obtains between the total phosphorus content of the whole corpuscles and the total white cell count or the volume of the white cell fraction of the corpuscles, both of which are very roughly proportional to the percentage of immature white cells.⁸

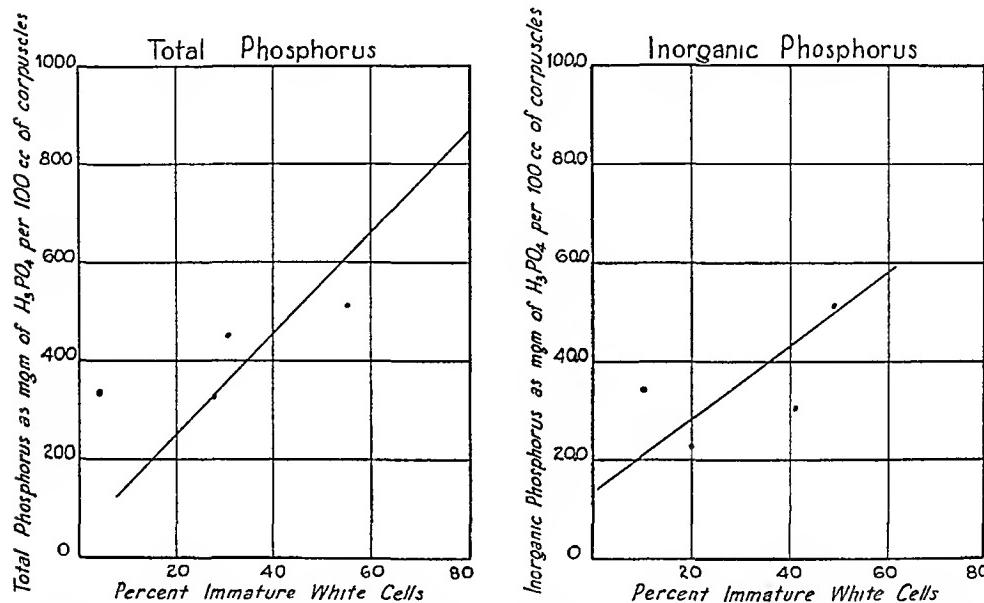


Chart 1—The relationship between the phosphorus content of the corpuscles and the percentage of immature white cells

The relationship between the immaturity of the white cells and the phosphorus content of the corpuscles is a similar one to that which obtains between the basal metabolic rate of the patient and the number of immature bone marrow cells, especially the leukocytes in the peripheral blood, as pointed out by Gunderson⁹ and substantiated by further observations at this hospital. These two relationships are represented together in Chart 2. Although the percentage increment in the basal metabolic rate of the patient and the percentage increment in the

⁸ It is not intended to imply here that any close parallelism exists between the total number of white corpuscles per cubic millimeter of blood and the percentage of immature white corpuscles. The association is only a very general one, and discrepancies are too numerous and too marked to permit the use of the count of the white cells in any given case as an index of the degree of maturity of these cells.

⁹ Gunderson, A. H. Boston M & S J 185 785 (Dec 29) 1921.

total phosphorus content of the whole corpuscles with increasing numbers of immature white cells follow somewhat different graphs, it is probable that both are different manifestations of the same phenomenon, namely, the presence in the blood of increased numbers of young cells. Of the two, the phosphorus content of the corpuscles is the more sensitive index of the degree of immaturity of the blood, inasmuch as the basal metabolic rate of the patient is undoubtedly influenced by compensatory factors operating to depress it.

2 The Early Effects of Short Wave-Length Roentgen Therapy on the Blood Phosphorus¹⁰—Observations on the blood phosphorus contents of

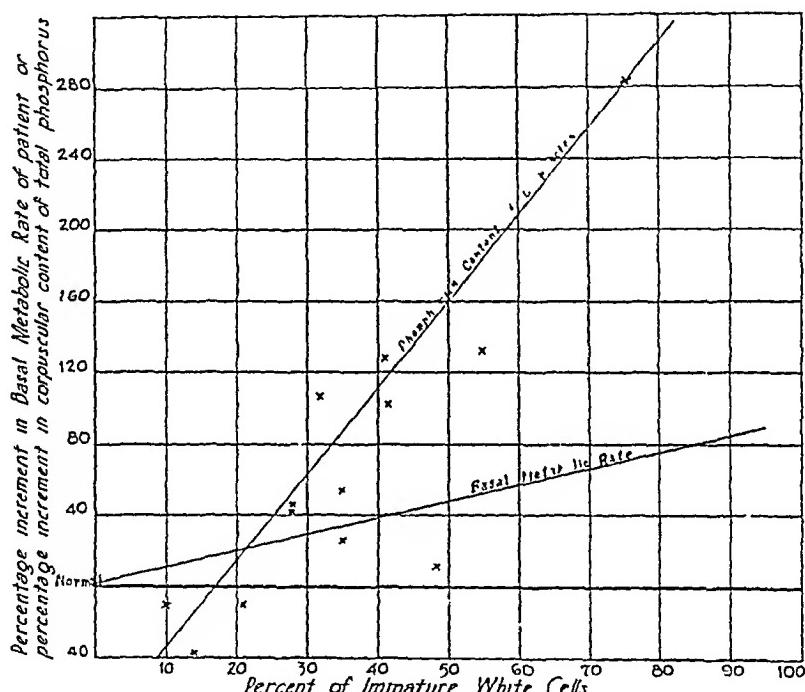


Chart 2.—The relation of the percentage increment in the total phosphorus content of the corpuscles and the percentage increment of the basal metabolic rate of the patient to the percentage of immature white corpuscles. The graph of the phosphorus content of the cells is the median obtained from the results shown in Table 1. The graph of the basal metabolic rate is the median obtained from Gunderson's data. The crosses represent values for corpuscular content of total phosphorus.

the patients with chronic myelogenous leukemia and cancer were made not only before irradiation and at periods remote from the time of therapy, as stated in the foregoing, but also at intervals varying from a few hours to many days following the application of the roentgen rays. Concerning the effects of irradiation that occur within a few hours

10 In each instance the high voltage, constant potential, short wave length roentgen ray described by Duane (Am J Roentgenol 9:781, 1922) was used. As a rule, from three to four exposures on successive days were given. The average dose of each exposure was about 600 electrostatic unit seconds, exclusive of secondary radiation.

TABLE 2—The Phosphorus Content of Blood in Myelogenous Leukemia and Cancer Before, During and Following Short Wave Length Irradiation Therapy¹

Case	Diagnosis	Date	Per Cent Inorganic Acid						Inorganic Phosphate Acid in 100 Ue		
			Red Blood Cells in Millions	Hemo- globin, per Cent	White Blood Cells in Thou- sands	Total Phosphoric Acid in 100 Ue	Plasma	Cells	Whole Blood	Plasma	Cells
13	Chronic myelogenous leukemia ¹	9/20	Roentgen ray treatment	4.1	65	270	28	155.7	22.7	318.9	31.5
		9/21	Roentgen ray treatment			270		224.1	37.2	472.0	29.0
		9/22				176	11	149.0	43.6	306.0	22.9
		9/24	Roentgen ray treatment	4.9	91	54	6	113.1	52.4	187.3	25.5
		9/25	Roentgen ray treatment								
17	Chronic myelogenous leukemia	9/27		5.4	110	29	6	134.2	57.7	231.0	22.1
		10/4		3.9		10	14	75.0	24.6	165.0	10.3
		2/28	Roentgen ray treatment	3.3	60	353	32	245.2	39.8	463.0	30.1
		2/29	Roentgen-ray treatment	3.7	65	304	30	320.1	27.4	738.0	29.7
		3/1		3.6		252		135.2	30.6	270.5	22.4
14	Chronic myelogenous leukemia	3/2		3.4	75	160	20				
		3/3		69	133	7					
		3/14		4.3	82	18	3	102.6	46.5	209.2	12.4
		3/19	Roentgen ray treatment	3.3	58	281	55	236.4	32.7	514.4	31.6
		3/20	Roentgen ray treatment	3.0	68	168	34	127.1	39.7	327.7	22.5
6	Chronic myelogenous leukemia ¹	3/21	Roentgen ray treatment								
		3/23				65	99	11			
		3/24		3.4	79	47	3				
		3/26		2.9	82	22	7	96.5			
		3/28		3.4	81	7	5				
10	Chronic myelogenous leukemia ¹	10/15	Roentgen ray treatment	4.7	75	119	28	140.0	18.5	316.0	11.1
		10/16	Roentgen ray treatment	4.9	84	112	12	157.0	22.3	319.0	18.2
		10/17	Roentgen ray treatment	4.7	72	81	18	137.0	26.9	264.0	16.2
		10/24		4.3	88	13	7	116.0	16.0	270.0	10.3

16	Chronic myelogenous leukemia.	8/27	Roentgen ray treatment	3.5	325	32.5	120.0	20.0	226.0	23.0	12.0	39.0	
		8/29	Roentgen ray treatment	2.9	70	21.0	20	225.0	46.5	50.0	23.0	13.5	
		9/7	Roentgen ray treatment	4.2	82	15	20	95.0	30.5	250.0	9.0	8.0	
3	Chronic myelogenous leukemia	12/3	Roentgen ray treatment	3.9	90	50	20	90.0	24.0	190.0	10.0	8.0	
		12/4	Roentgen-ray treatment	1.00	45			220.0	68.5	436.0	10.5	12.5	
		12/5	Roentgen ray treatment	5.1	103	30	12	165.0	22.0	360.0	13.0	12.0	
		12/6		90	25	17.5	120.0	32.0	225.0	12.5	13.0	12.0	
		12/11		4.5	102	30	12.5	110.0	21.5	225.0	9.0	7.0	12.0
20	Cancer of the breast	11/4		4.2	97	6.3							
		11/5	Roentgen-ray treatment	4.4	97	5.1							
		11/6	Roentgen ray treatment	4.6	97	6.4							
		11/7		4.6	97	6.4	120.0	42.0	225.0	12.5	12.0	11.5	13.2
21	Cancer of the breast	11/12	Roentgen-ray treatment	4.9	98	11.1							
		11/13	Roentgen ray treatment	4.9	99	12.2							
		11/14		4.6	97	6.8							
		11/16		5.0	104	18.3							
22	Cancer of the breast	10/22	Roentgen ray treatment	6.1	103	8.2							
		10/23	Roentgen ray treatment	5.4	110	9.2							
		10/24	Roentgen-ray treatment	4.7	104	8.5							
		10/26		4.4	106	8.1							
		11/8		5.0	110	9.4							
		11/15											
23	Cancer of the stomach	10/26	Roentgen-ray treatment	4.3	68	20							
		10/27	Roentgen-ray treatment	4.5	72	21.6							
		10/29		3.9	68	17.8							
		11/15		5.2	77	15							
		2/21		3.8	78	10.7							
		2/22	Roentgen-ray treatment	4.6	88	13.8							
		2/25	Roentgen-ray treatment	8.8	72								
		2/28											

* In each case, the determinations on the blood were made prior to the roentgen ray treatment, in many of the cases, this was done on the same day that the treatment was given

following exposure, the data accumulated show too many and too extreme variations to warrant any conclusions at present. These data are not reported. The course of events following the initial disturbances due to irradiation is represented, however, in Table 2, in which are shown the findings in the five cases of cancer and in six typical cases of chronic myelogenous leukemia. Even these observations together with those on the other thirteen cases of leukemia do not permit of an entirely satisfactory recapitulation. Nevertheless, certain definite tendencies both in the cases of cancer and in the cases of leukemia are evident.

Within twenty-four hours following the first exposure to irradiation in a given series of treatments there occurs, generally, an initial rise in the level of the total phosphorus content of the plasma and, frequently, a rise in the total phosphorus content of the corpuscles. These initial elevations may be followed within a day or two by sharp declines to normal or even subnormal levels of total phosphorus values for both plasma and cells.

Following subsequent exposures to irradiation in the same series of treatments, the total phosphorus content of the plasma usually rises again above the upper normal limit (about 35 mg per hundred cubic centimeters) or, should it not have fallen following the first exposure, it rises to still higher levels provided that the value for the total phosphorus content of the plasma was below the upper normal limit at the time the first treatment was given. Under such circumstances the total phosphorus content of the cells continues to fall. But if the value for the plasma content of total phosphorus, especially at the time of subsequent treatments, is above the upper normal limit, then it is generally true that following subsequent treatments the total phosphorus content of the plasma remains stationary or falls, whereas the total phosphorus content of the cells rises and this rise in the cell phosphorus is maintained until such a time as the plasma phosphorus has declined to values within normal limits.

The inorganic phosphorus contents of the plasma and cells, though subject to marked variations, show a distinct tendency after irradiation to approach normal or subnormal values as the abnormal and excessive numbers of formed blood elements

The alterations after irradiation in the total and inorganic phosphorus of the whole blood and cells in leukemia are much more striking than those observed in cancer. However, the changes that occurred in the cases of cancer, though relatively slight, were similar to those in the cases of leukemia and serve but to emphasize the before mentioned generalizations regarding blood phosphorus following irradiation. In a patient with cancer, irradiation at first causes a decrease in the leukocyte count and a decrease of immature blood cells, as it usually does to a

vastly greater degree in leukemia. It is to be noted that both in leukemia and cancer the corpuscular phosphorus may actually rise, in the former, markedly, in the latter, very slightly after irradiation in the face of a falling white cell count and a falling percentage of immature bone marrow cells.

Although it is impossible in the present state of our knowledge to explain the fluctuations in the values for inorganic phosphorus in the blood following irradiation in cancer and leukemia, it is suggested that the following explanation might account for the observed changes in the total phosphorus contents of the corpuscles and plasma. The destruction of cells incident to irradiation and certainly not confined to the blood cells results in the liberation and excretion of large amounts of phosphorus. This phosphorus may be largely or wholly taken up by the plasma, provided the conditions for elimination are favorable, as evinced by the finding of a normal plasma content of phosphorus before treatment. But if cell destruction has been excessive, or if, as shown by an abnormally high phosphorus content of the plasma before treatment, conditions for elimination are unfavorable, then the liberated phosphorus may be stored temporarily in the corpuscles and particularly in the red blood corpuscles, until the excess of phosphorus in the plasma has been eliminated. This conception is in part borne out by the work of Ordway, Tait and Knudson¹¹ who found the increase in the phosphorus content of the urine after irradiation to be sustained, particularly in myelogenous leukemia, even after the blood histology had become approximately normal.

MORE REMOTE EFFECTS OF IRRADIATION

It has been shown⁴ that barring those conditions in which the phosphorus metabolism is truly disturbed, the total phosphorus content of the whole blood is a function of its hemoglobin content. As in other conditions, so it is in chronic myelogenous leukemia when, through irradiation therapy, or otherwise, the white corpuscles have been reduced to normal and the early effects of irradiation have subsided. This trend of events is illustrated by the cases represented in Chart 3. In this chart the heavy line indicates the ideal values for the total phosphorus content of the whole blood for different levels of hemoglobin, as previously determined by us.⁴ The numbered lines represent the actual course of the total phosphorus following irradiation, in each of four of the leukemia cases and in two of the cases of cancer.

The values for the total phosphorus content of the whole blood (ordinates) are plotted against the values for the hemoglobin content of the blood (abscissas). The chart shows that both in the cases of

¹¹ Ordway, T., Tait, Jean, and Knudson, Arthur. Albany M Ann 41: 1 (Jan.) 1920.

cancer and leukemia the actual values for total phosphorus in the whole blood approach the idea values, in the former before irradiation and again as soon as the disturbances incident to irradiation have subsided, in the latter as soon as the total number of white corpuscles and the immature white corpuscles have been reduced to essentially normal levels.

In leukemia, this reduction of the number and immaturity of the white cells is evident very shortly following exposure to irradiation, and is usually complete in from five days to a few weeks thereafter. Thus the blood remains during remission. Finally, as relapse occurs, as illus-

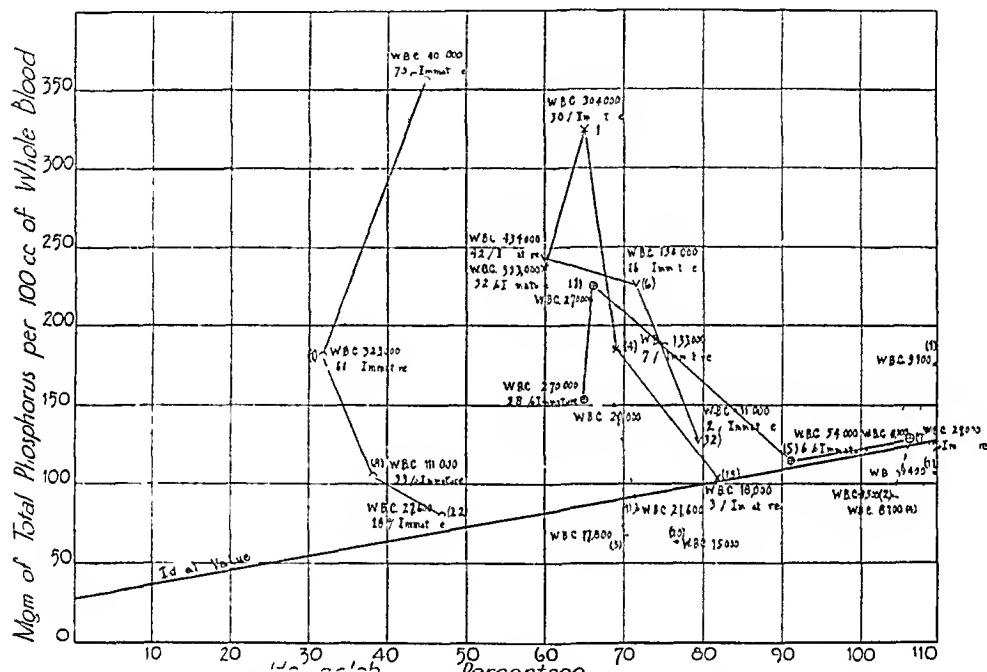


Chart 3—The relationship between the total phosphorus content of the whole blood and the percentage hemoglobin content of the blood in two typical cases of cancer (dotted lines) and four typical cases of chronic myelogenous leukemia (solid lines). The small numbers refer to number of days elapsed since first exposure to irradiation therapy. No number is appended to observations made before exposure to irradiation.

trated by Cases 1 to 9 inclusive, the blood phosphorus values increase and again become determined largely by the same factors (immaturity of cells, volume of cells, etc.) which had controlled them before exposure of the patient to irradiation.

SUMMARY

1 A study of the blood phosphorus was made in nineteen cases of chronic myelogenous leukemia and in five cases of cancer before, during and following roentgen-ray therapy.

2 In nonirradiated or not recently irradiated cases of chronic myelogenous leukemia, the total phosphorus content of the whole blood is

markedly elevated. This increase is due almost entirely to the increased total phosphorus content of the corpuscles. The mean value for the total phosphorus content of the plasma, in spite of wide individual variations, was found to be within normal limits.

3 The total phosphorus content of the corpuscles in chronic myelogenous leukemia is dependent in part on the number of white corpuscles present, but particularly on the number of immature myeloid cells, especially white corpuscles.

4 Relationships are illustrated between the numbers of immature cells in the blood and the basal metabolic rate of the patient, and between them and the corpuscular content of total phosphorus. The total phosphorus content of the corpuscles is a more sensitive index of their immaturity than the patient's basal metabolic rate.

5 Changes in the blood phosphorus occur as a result of roentgen-ray therapy given to a patient with leukemia or cancer. As a result of tissue destruction incident to such treatment, a transient, but often, in leukemia, a marked increase of the total phosphorus content of both plasma and cells generally occurs, the latter apparently serving as a temporary reservoir for the excess of phosphorus, which for the moment cannot be taken care of by the plasma.

6 In chronic myelogenous leukemia, when the initial disturbances following irradiation have subsided, the corpuscular content of total phosphorus falls to normal levels as the numbers of immature cells in the blood stream diminish. Thereafter, as long as the numbers of white cells and immature cells remain within essentially normal limits, the total phosphorus content of the whole blood is in proportion to the percentage hemoglobin content, as is the case in other conditions.

7 No significant variations were noted in the inorganic phosphorus contents of plasma or corpuscles before, during, or after roentgen-ray therapy in leukemia or cancer.

THE PROGNOSIS OF CHRONIC INFECTIOUS ENDOCARDITIS*

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The John Jay Borland Fellow in Medicine, 1923-1924

CHICAGO

According to reports in the literature, chronic infectious endocarditis is usually fatal Billings,¹ observed only one recovery in fourteen patients, and all of the ten reported by Osler² died. Of the 150 patients with subacute bacterial endocarditis reported by Libman,³ 146 died, and recently Thayer⁴ reported 206 cases terminating fatally. Contrasted with these are other statistics mentioning a lower death rate. Four patients treated with sodium cacodylate by Capps⁵ are reported well after three years. Graham, Ollie and Detweiler⁶ have observed twenty-three patients for a period of nine years, and of these at least twenty are living. The presence of bacteria in blood cultures of patients with endocarditis is generally regarded as indicating a grave prognosis. This idea is not altogether in harmony with results obtained at St Luke's Hospital, Chicago. Of fifty-seven patients with bacterial endocarditis twenty-four are living and many of them seem to have recovered from the heart valve infection. The other thirty-three are dead.

CLINICAL DIAGNOSIS

Any discussion of the results of bacterial endocarditis obviously hinges on the proper clinical diagnosis of the disease. A progressive valvular lesion, fever, and the clinical signs of embolism of the brain, spleen, or kidneys are important symptoms, but in order to make the diagnosis certain, these clinical manifestations need to be supported by recovering the specific bacteria in cultures from the blood of such patients. In fact, demonstrating bacteria in the blood by cultures is probably the most conclusive evidence of an infectious endocarditis.

*From the Medical Service and Pathological Laboratory of St Luke's Hospital, Chicago.

1 Billings Arch Int Med **4** 409, 1909

2 Osler Quart J Med **2** 219, 1909

3 Libman, Emanuel Characterization of Various Forms of Endocarditis, J A M A **80** 813-818 (March 24) 1923

4 Thayer, W S Symposium on Endocarditis, J A M A **82** 1721 (May 24) 1924

5 Capps, J A Am J M Sc **165** 40 (Jan) 1923

6 Graham, Duncan, Ollie, J A, and Detweiler, H K Further Report on Patients Who Recovered from Subacute Bacterial Endocarditis, J A M A **82** 1721-1722 (May 24) 1924

In the number of patients herein reported with chronic infectious endocarditis studied at St Luke's Hospital, pathogenic bacteria were recovered by cultures of the blood of each one. Each one had a heart murmur. All had fever not explained by extracardial lesions, and many had an anemia and the clinical signs of embolism.

Almost all of the twenty-four patients living are without fever and other signs of infection, and many of them are able to do light work. One has been well for thirteen years, two for seven years, and one for two and a half years. Thirteen are in the second year and seven are in the first year of clinical observation.

The clinical progress of the patient who died differed markedly from that of those living. This difference has made possible a prediction regarding the outcome soon after the disease is recognized. Those who died had a higher fever and more marked symptoms of sepsis. Twenty-six of the thirty-three had a prolonged irregular septic type of fever, the temperature ranging from 101 to 105 F. Twelve of these thirty-three had chills. Of the twenty-four living, none had fever exceeding 101 F., the maximum being from 99 to 100 F., except during an intercurrent infection. The clinical record of none of these mentions chills.

Anemia and symptoms of embolism occur in the patients of each group. But the anemia is usually more pronounced, and symptoms of embolism are more frequent in those of the septic type. The urine of twenty of the thirty-three who died contained red blood cells, twelve had petechiae of the skin, twelve a palpably enlarged spleen, eleven a severe anemia (red blood cells 3,500,000 or less, hemoglobin 65 per cent or less), five painful cutaneous nodes, three retinal hemorrhages, two hemiplegia, and two club fingers. Of the twenty-four living, in only eight were there red blood cells in the urine, three had petechiae of the skin, four a palpably enlarged spleen, seven a marked anemia, none had painful cutaneous nodes or retinal hemorrhages, three had hemiplegia and none club fingers.

Although blood was often found in the urine of patients with the milder type, the red corpuscles in the urine of these patients were present in smaller numbers and only after repeated examinations. In contrast to this, blood was found more regularly and in larger quantities in the urine of the patients who died.

MODE OF ONSET

The mode of onset is noteworthy. In the fatal group there is a rapid development of weakness and anemia, with fever of the septic type and often with signs of cardiac decompensation. A chill or symptoms of an embolus, in a few instances, is the first manifestation of the

disease The onset of the disease in the twenty-four living patients was in no instance marked by a chill and was accompanied, as before mentioned, by a lower fever

Acute polyarticular rheumatism was associated with the endocarditis in ten of the patients with the milder type Whether the arthritis preceded or followed the endocarditis was usually difficult to determine The endocarditis seemed to be the antecedent in one patient From a clinical standpoint the disease in many of this group cannot be distinguished from a rheumatic endocarditis The onset of the disease of fourteen patients with the milder type was not associated with arthritis Only four of the thirty-three patients who died had an active arthritis during the fatal attack of endocarditis

BLOOD CULTURE

The number of bacteria in the blood stream is greater in the fatal cases Repeated cultures of the blood from those with the milder type was usually necessary before the specific bacteria were recovered and even then the colonies were few On the contrary, as a rule, bacteria were recovered more easily and in much greater numbers from patients with the septic type There were, however, some exceptions to the latter statement

The disease in several patients at first was considered of the milder type For a few months the patients were without fever and then the disease recurred with septic manifestations and ultimate death

The causal organism in fifty-four of the total fifty-seven patients with chronic infectious endocarditis was *Streptococcus viridans*, in one a hemolytic streptococcus of the ordinary type, in two an alpha hemolytic streptococcus

Thirty-five of the fifty-seven patients were treated with sodium cacodylate Three grains of a freshly prepared solution were given intravenously daily during a period of from eight to sixteen weeks Eighteen of those so treated are dead and seventeen are living, a death rate of 51 per cent Another group of twenty-two patients not treated serves as a comparison Of these, seven are living and fifteen are dead, a death rate of 68 per cent As a patient with chronic infectious endocarditis cannot be considered permanently well until two or three years after the onset, conclusions regarding the merits of any medication with this disease cannot be made until a longer period of observation has been reached

Archives of Internal Medicine

VOLUME 35

APRIL, 1925

NUMBER 4

THE LIFE CYCLE OF PEPTIC ULCER *

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Notwithstanding years of intensive clinical study of the etiology, pathology, course and effects of treatment of chronic peptic ulcer, many points are still open for discussion. The advent of roentgenography has given a renewed impetus, opening up afresh, as moot questions, problems that apparently had been satisfactorily answered. The recent contributions of roentgenologists have tended to show that under favorable circumstances many ulcers tend to disappear and presumably to heal, the disappearance of the roentgenographic niche being the criterion on which such a judgment is founded.

On the other hand, the operation of subtotal gastrectomy for the radical removal of ulcer, an operation that seems likely to enjoy an increasing and a well warranted sphere of activity, has delivered into our hands fresh ulcer specimens of various types and at various stages in the life cycle of the peptic process.

These two factors alone have contributed considerable new information concerning the pathology, the course of the treated and of the untreated ulcer, the healing of the ulcer, and the conditions for its recurrence after incomplete cure. In the light of these new data, we may be privileged to reexamine the subject of the life history of ulcer, particularly from the standpoint of the healing of such a process after conservative medical, or after surgical, treatment. In particular, we are interested in the problem of what happens to a peptic ulceration in the stage of intermission of symptoms. Do ulcers ever spontaneously heal? Does an ulcer heal temporarily and partially when the patient enters a period of freedom from symptoms and the niche disappears? How often is such a healing process a durable and lasting one, and what are the pathologic stages in such a restitution to integrity? What are the conditions incident to the recurrence of ulcer? And, finally, to what extent do the usual surgical procedures vouchsafe lasting prevention of recurrence of the original or of new ulcers?

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From the mass of varied opinions, one fact seems to stand unchallenged, and that is that ulcers can and do heal. Stewart,¹ detailing the necropsy findings at the Leeds General Infirmary for the years 1910 to 1921, states that the "healing of gastric and duodenal ulcer is a common event." His statistics show that, in the postmortem room, scarring in the stomach is encountered almost as frequently as ulceration, while duodenal scars occur with about half the frequency of duodenal ulcers. Hart² found in general necropsy material in Germany that from 8 to 13 per cent of adult bodies carry either open ulcerations or scars of healed ulcers, the scars and the ulcers occurring with about equal frequency. These statistical data are corroborated by many of the most representative pathologists, including Aschoff. We are therefore bound to accept the fact that, under satisfactory conditions, ulcers can and do heal in a certain percentage of cases. It remains for us to reexamine our material and to determine the required conditions for bringing about such a desired termination. But necropsy material is unsatisfactory in that it represents only an end stage of an ulcer or often an ulcer found accidentally during an examination in a case in which death has been due to some intercurrent disease. The gastric symptoms are in the background, probably not observed or noted, and new clinical knowledge of the life cycle of ulcer is not easily deducible.

On the other hand, in all clinics in which the operation of subtotal gastrectomy is being performed for ulcer, we have at hand many fresh specimens of ulcer removed at various stages in the cycle of life of the process, for instance, at the height of an attack, or after hemorrhage, or during the intermission stage, or just at the beginning of a recurrence. This constitutes today most valuable material for a review of the whole subject, and in many of the clinics of Europe (Askanazy,³ Perman⁴) where such material has come to hand, such studies have been begun.

We have been so fortunate as to have had the privilege of prosecuting such investigations. The material at our disposal consists of approximately seventy specimens, each specimen consisting of the distal one third or one half of the stomach and adjoining first portion of the duodenum, including the ulcer itself. By correlating the clinical history with the pathologic picture of the ulcer, by bearing in mind the roentgen-ray evidence of healing, and by observing the incidence and frequency of recurrence of ulceration, we can add further valuable data to that at hand.

1 Stewart, M. J. Brit. M. J. 2: 1164 (Dec. 16) 1922; ibid. 2: 955 (Nov. 24) 1923.

2 Hart. Mitt. a d. Grenzgeb. d. Med. u. Chir. 31: 291, 1918-1919.

3 Askanazy. Virchows Arch. f. path. Anat. 234: 111, 1921.

4 Perman, E. Acta chir. Scandinav. 55: 286, 1923.

In addition, the medical wards of the hospital and the follow-up system in the outpatient department have given us ample and much opportunity to observe, if only for a limited time up to date, the end-results of medical treatment. Clinical medicine and medical and surgical therapy being represented and pieced together, the sum total gives a good impression of the life history of a peptic ulceration.

PATHOLOGY OF A GASTRIC ULCER COMPARED WITH ITS CLINICAL HISTORY

If we study the specimens of gastric ulcer from cases in which there has been absolutely no previous gastric complaint and in which the history is of only a few weeks' duration, the onset of the symptoms abrupt, with severe pain, vomiting and rapid loss of weight, we are led to the belief that such typical peptic ulcers can and does form within a few weeks. The shortest history of such a case in our experience is three weeks. The ulcer in this instance was approximately 1 by 3 cm in diameter, and had all the appearances of a chronic penetrating ulcer (Fig 1), it had undermined edges, thickened walls, and its base was constituted of a thin remaining layer of muscle and the slightly thickened serosa. Grossly and microscopically, in size and in shape, it had every characteristic of a penetrating peptic ulcer of long standing, except that there was little evidence of dense, cicatricial, connective tissue proliferation. Another ulcer, of four weeks' duration, had achieved a size of 2 by 3 cm, and represented a large crater with overhanging edges, a typical Cruveilhier ulcer.

Another group of specimens studied were those in which remissions alternated rapidly with attacks. In all of these cases, the recent history was one of almost continuous severe complaint without relief. These ulcers all ranged in size from 1 to 1.5 cm, and had an appearance identical with those in the previous group. There was no evidence of healing (Fig 2).

From these two groups of specimens, we are led to believe that ulcers form rapidly, probably within two or three weeks, and, having by that time achieved a given size, no longer extend their circumference. They react only by an increase in protective connective tissue in the periphery and in the depths. This also would agree with the idea that perforation as well as hemorrhage usually are observed in cases with a history of only a few days or a week, namely, in the stage of rapid penetration. A far smaller percentage of chronic indurated ulcers of long standing give rise to sudden surgical perforation with peritonitis.

The largest ulcer we have seen, one that was 1.5 by 3.5 cm in diameter, occurred in a man whose history was that of one year of continuous severe gastric complaints without intermission (Fig 3). It

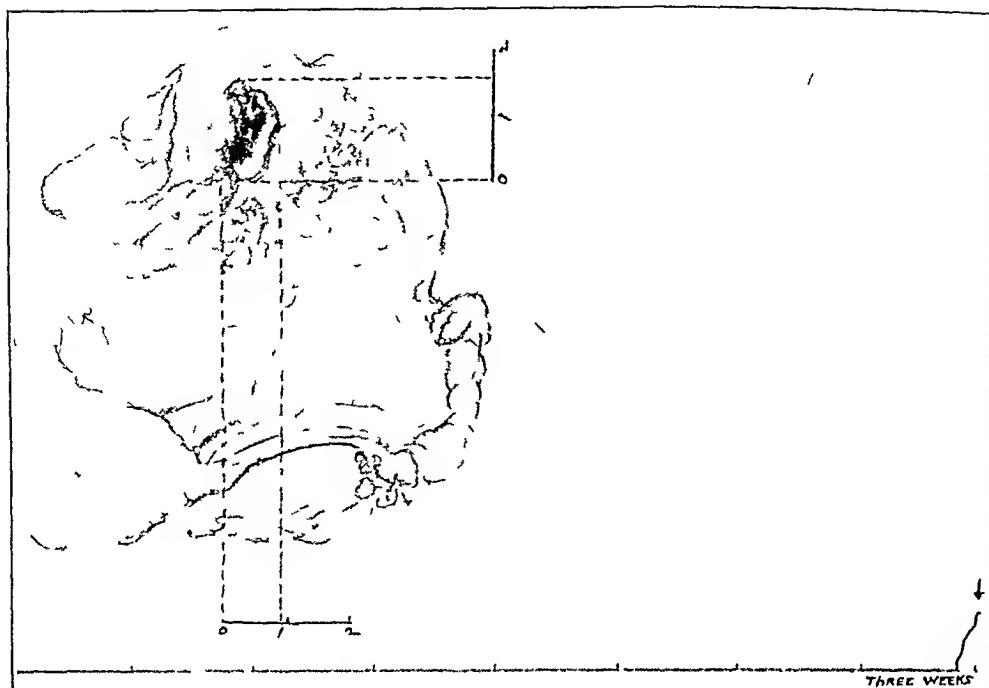


Fig 1.—Penetrating ulcer of lesser curvature, deep, punched out, 15 by 1 cm, with sharp edges, muscularis base and marked induration. The patient, a man, aged 38, with no previous history of ulcer, began, three weeks before operation, to have severe epigastric pain one-half hour after eating. He had vomited once or twice and lost 15 pounds (68 kg) in weight.

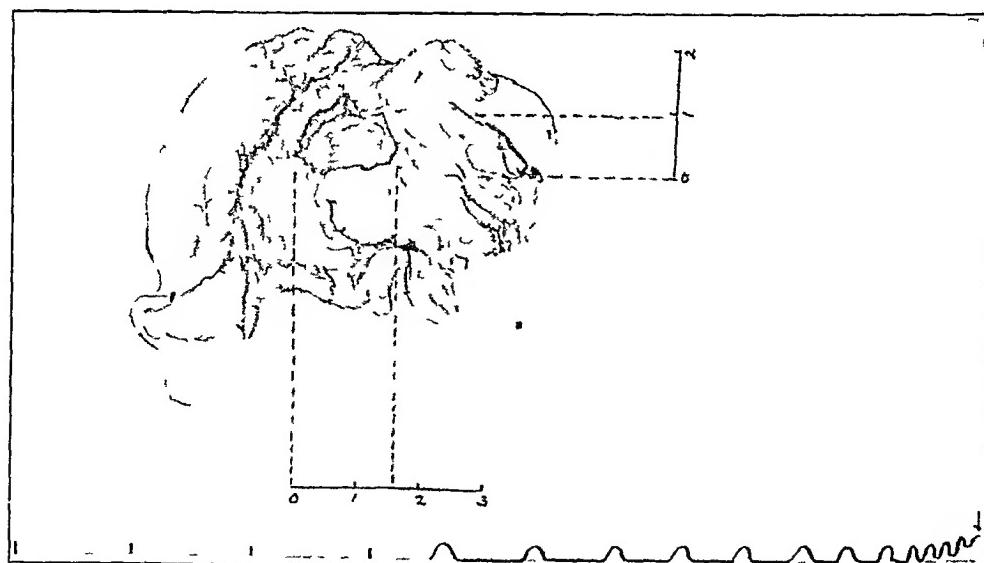


Fig 2.—Penetrating ulcer of lesser curvature near pylorus, punched out, with overhanging edges, 15 by 2 cm, muscular coat showing in the depth, blood vessels exposed. The patient, a man, aged 50, with a history of many years of typical gastric symptoms, had been much worse during the last few months, suffering a marked loss in weight.

is important to note that ulcers with continuous symptoms are larger, deeper and more dangerous than those in the preceding class in which attacks alternate with free intervals. A priori, one would surmise that in the intermission period a sufficient reparative process often takes place to prevent an extension of the pathologic ulceration.

In addition to this, there is a group in which the history was one of years, but in which long periods of freedom from pain were followed by shorter spaces of periodic activity of the ulcer. These ulcers were small, usually 0.5 by 0.5 cm in diameter, superficial, and apparently had a firm connective tissue bed. These are ulcers showing a tendency to slow cicatization.

Finally, there is a group of specimens of hour-glass deformity of the stomach. The specimens have a history of from one to twenty years. An open indurated ulcer has perforated the viscus, the base of the ulcer being formed by a neighboring organ, usually the liver. The crater is wide open, the base patulous and fixed to the liver. The ulcer has not healed, it is unable to contract because its base is fixed and unyielding. The productive reaction on the part of the ulcer results only in a thick callous ulcer with connective tissue strands infiltrating the serosa and encircling the viscus (Fig 4). The result is the bilocular deformity. There is evidence of much and continued tendency to heal, resulting only in more deformity and failure to fill the crater with granulations. This does not necessarily preclude eventual healing, but certainly delays it indefinitely.

PATHOLOGY OF DUODENAL ULCERS COMPARED WITH THEIR CLINICAL COURSE

Duodenal ulcers have more of a tendency to be cast in one mold. Most of those seen in specimens removed at operation are smaller, about 0.5 by 1 cm in diameter, rather shallow, with muscularis as a base, and show little tendency to productive cicatricial repair. In the case with the shortest history, four months, a fully developed ulcer was noted.

However, in the cases in which the intervals in the history have been longer than the periods of pain, a heaping up of inflammatory scar tissue may be distinctly seen. The largest ulcers were those in which the recent course, or the course from the onset, had been the most severe and the most continuous. Secondary diverticulum formation, as described by Akerlund,⁵ is very common. It is in the nature of a pulsion diverticulum and occurs between the site of the ulcer and the pyloric sphincter. It occurred in every fourth or fifth specimen removed at operation.

⁵ Akerlund Roentgenologische Studien Über den Bulbus Duodenum, 1921

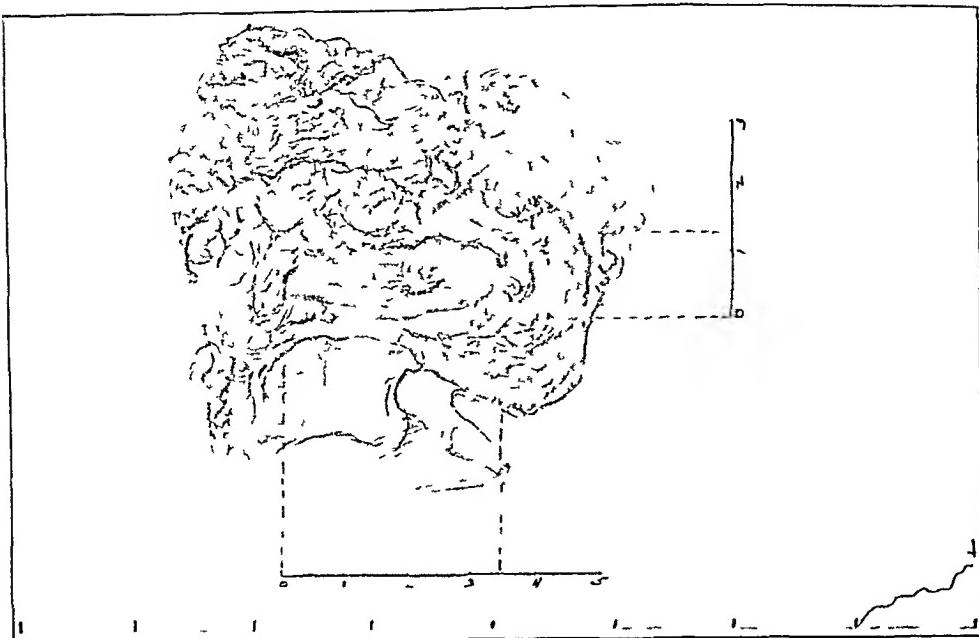


Fig 3—Large, oval, callous perforated ulcer at reentrant angle on lesser curvature. The patient, a man, aged 65, had a history of constant pain of increasing severity, of one year's duration, with marked exacerbation during the last two weeks, marked by severe pain and vomiting.

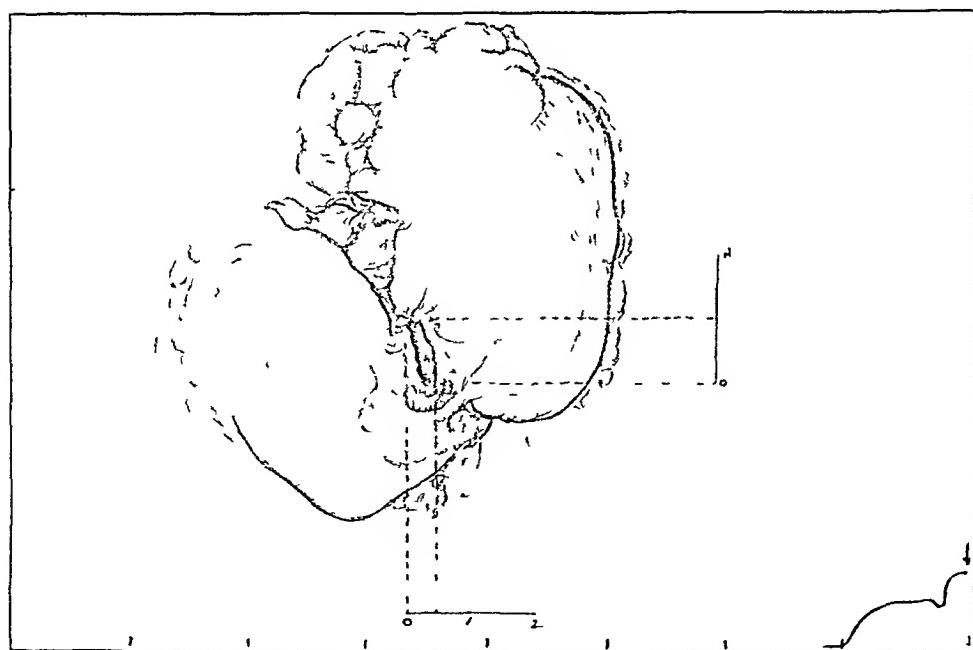


Fig 4—Specimen from subtotal gastrectomy for hour-glass stomach. The patient, a woman, had had symptoms for one year of epigastric pain, beginning twenty minutes after eating and lasting from two to three hours, which were relieved by bicarbonate. One month before admission, the pain became more severe and constant, and the patient lost 15 pounds (68 kg) in weight. A test meal showed a high gastric acidity.

In a case of three years' duration in which the free intervals had been as long as six months, a small, puckered but open ulcer, 0.2 by 0.6 cm, was all that remained of the original ulcer. A large diverticulum was present between the ulcer and the pyloric sphincter (Fig 5). The small size of this ulcer, in comparison with the long history, speaks for a well advanced reparative process. In another

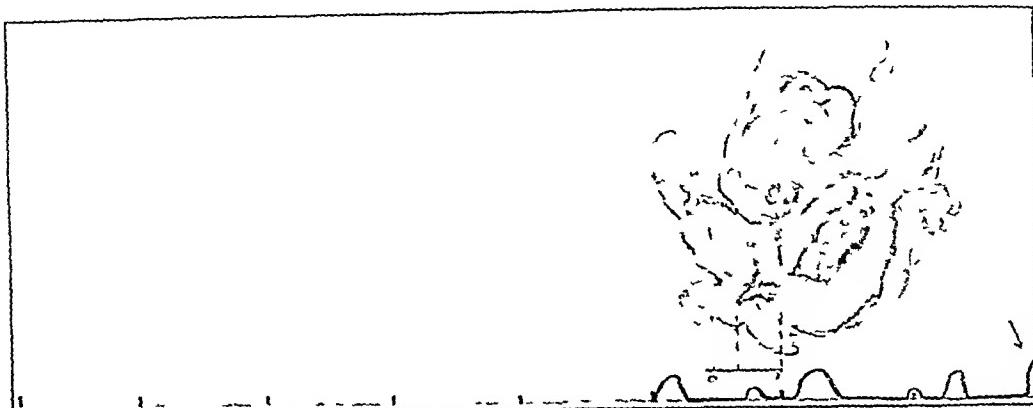


Fig 5.—Penetrating ulcer of duodenum, with secondary diverticulum formation, small, scooped out, 2 by 4 mm. The patient, aged 37, had had pains for 3 years at irregular periods, with remissions as long as six months. The present attack began three weeks before

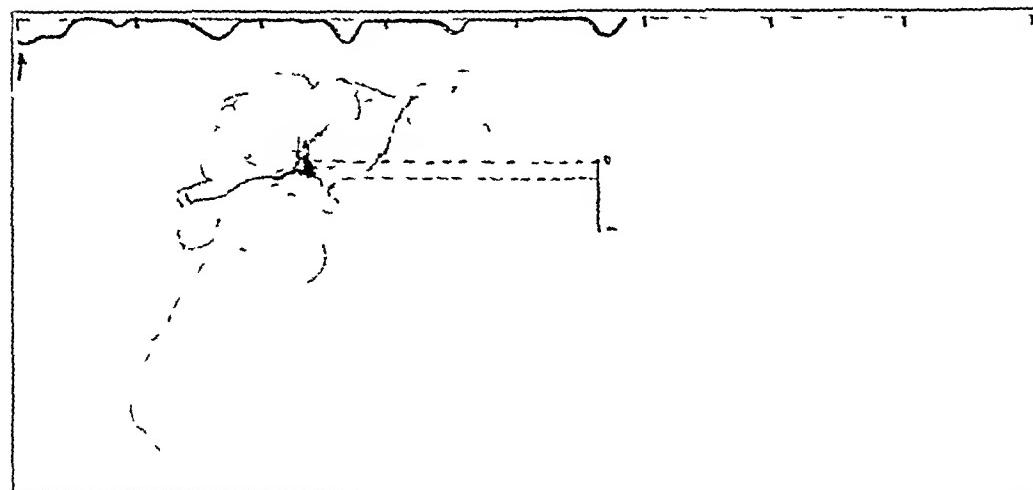


Fig 6.—Simple duodenal ulcer. The patient had cramps of five years' duration, the attacks being mild with long intervals of remission

case, of twenty years' duration, with mild intermittent symptoms, the ulcer was only 0.3 by 0.5 cm in diameter. Again, a very large diverticulum was present. Apparently, the diverticulum was associated with cicatricial contracture in the walls of the ulcer.

Two cases, with five and twelve year histories in which there were periods of relief up to one year in duration, showed only a small, puckered ulcer, 2 by 3 mm in diameter, with a shallow base (Fig 6). Let

us not be understood to say that these ulcers had healed, there was a distinct, persistent loss of community of the surface mucosa, but there was also undoubted evidence of connective tissue repair taking place and contracture of the walls of the ulcer, both in depth and in circumference.

There remains for consideration a group of seven cases of duodenal ulcer in which, at the time of operation, the ulcer had either healed, pathologically speaking, or almost healed. This group was most interesting. The operative indications were clear cut. Most of these were cases in which a severe hemorrhage, endangering life, had occurred a few weeks previously. One was a case of recurring gastric tetany, and one was a case of repeated recurring ulcer attacks, in which the patient pleaded for permanent relief by surgical intervention. The cases in which profound hemorrhage almost to exsanguination had occurred were allowed several weeks in which to permit the regeneration of the blood elements and of the general strength of the patient. Following hemorrhage, it is almost a uniform rule that the gastric symptoms cease for a longer or shorter period. A modified Sippy diet was administered during the weeks following the hemorrhage. In the specimens removed at operation, the remains of the ulcer could usually be identified only as a small scar or a puckered area with regenerated mucous membrane. The same held true for the case of tetany.

The duration of the clinical symptoms does not seem to be of great significance, for some of these cases were five years or more in duration, the attacks, however, alternated with long periods of relief from symptoms.

The tendency of gastric ulcers to heal after hemorrhage is much less marked. Specimens of gastric ulcer after hemorrhage still show evidence of the erosion of the bleeding vessel in the base of the ulcer, and little in the nature of reparative reaction is visible.

In the phenomenon of the healing of duodenal ulcers after hemorrhage, one is faced by two contradictory facts. The ulcers show a definite tendency to heal and yet have given rise to severe hemorrhage. One can harmonize these facts only on the hypothesis that ulcers, or duodenal ulcers, heal readily in the intermission period, only to break down again and reulcerate with the next attack. It is only by such a hypothesis that one can explain such an apparent contradiction in facts. And yet, in this very phenomenon lies the explanation of what occurs in the intermission stage of the clinical history of ulcer, a tendency to heal followed by a reopening of the same or possibly of an entirely new ulcer with the next attack, another phase of healing and another recurrence of the ulceration. In some of these cases, final healing must take place, else we could not explain the postmortem discovery of gastric and duodenal scars. In probably a larger percentage of cases,

the extent and frequency of reulceration exceeds the phases of healing, until gastric surgery steps in and gives relief to the sufferer, or until a stenosis, or a fatal accident, hemorrhage or perforation, calls for operative cure.

This phase of healing and reulceration in the cases that are less amenable to medical treatment will again be discussed in connection with the roentgenographic evidence of the disappearance of the niche under medical treatment and its not infrequent recurrence. It is similarly seen in the healing of an ulcer after gastro-enterostomy, and in the not at

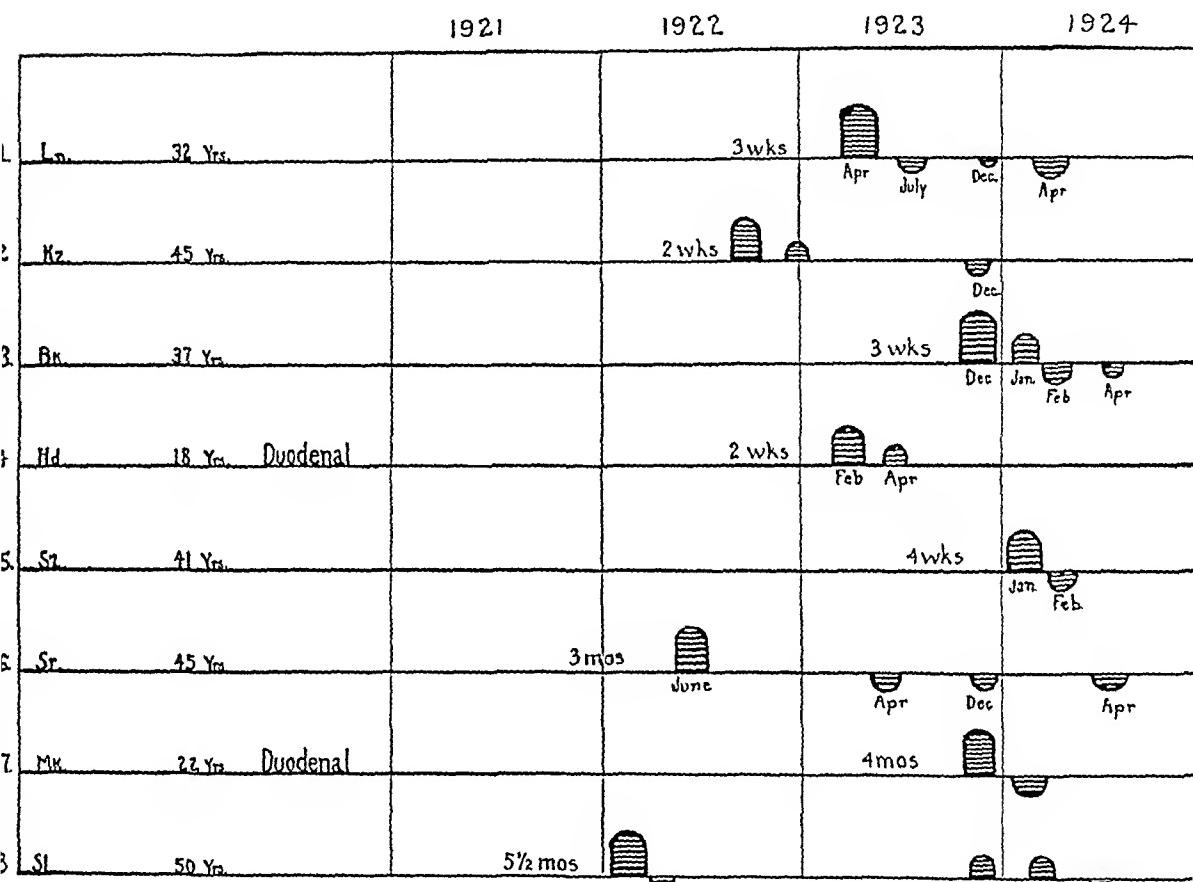


Fig 7.—Course of cases of penetrating ulcer observed with repeated roentgenographic examinations. In this and the succeeding charts, the elevation above the base line represents the observance of a "niche," the depression below the line indicates a negative roentgenographic report. The elevations are placed approximately in the year and time of the year when the examination was made. The reference to weeks, months or years indicates duration of symptoms before first roentgenographic examination.

all infrequent recurrence of the same ulcer or of a new ulceration months or years after the apparent surgical cure.

OBSERVATIONS ON REPARATIVE PROCESSES IN PEPTIC ULCER

Until the cause of peptic ulcer is discovered, and until the lesion can be reproduced in experimental animals at will, the pathologic details of

repair cannot be completely followed. It may be safely assumed, however, that the characteristic features of the ulcer are the result of two opposing influences (1) the causative, destructive factors which continue to operate, and (2) the protective reaction of the organism, the reparative factors. The histologic appearance of any individual ulcer, therefore, would seem to depend on which of these two influences is in the ascendant at the time the lesion is removed.

Specimens of approximately seventy-three partial gastrectomy operations during the last three years, performed for ulcer by Dr. A. A.

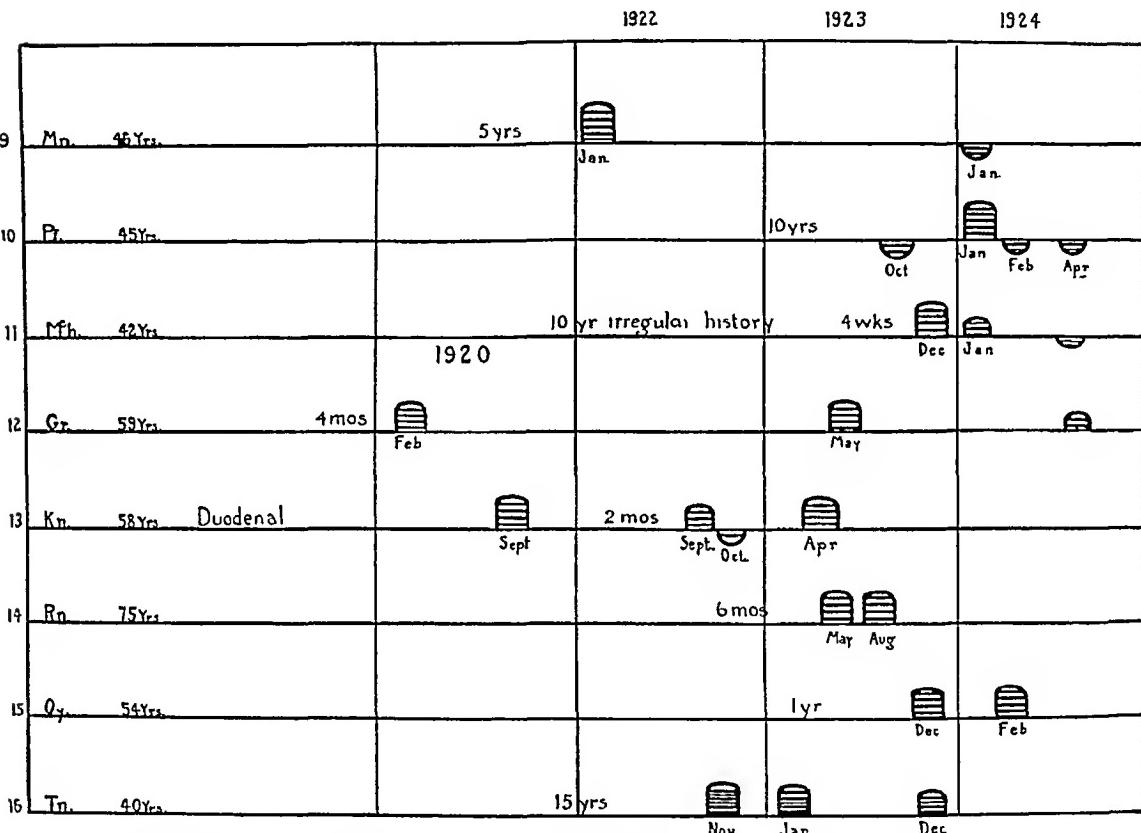


Fig. 8—Course of cases of penetrating ulcer observed with repeated roentgenographic examinations.

Berg or members of his staff, have been reviewed to determine, first, the histologic features of reparative processes, and, second, the frequency of their predominance. It should be pointed out that evidence of such predominance does not prove that the process would have gone on to completion in any individual instance.

In thirty-four specimens of gastric ulcers, there was no specimen in which healing was predominant. The lesions showed, in general, the characteristic picture of ulcer as described by Askanazy³ and Pernan.⁴ The mucosa about the ulcers showed inflammatory changes of the stroma, deformation and cystic dilatation of the glands, and an abrupt

loss of substance at the site of the ulcer. The latter presented an area of exudate overlying a zone of necrosis. The exudate consisted of mucus, fibrin, desquamated cells, leukocytes and round cells. The necrotic zone appeared to be granulation tissue or connective tissue, which stained poorly and was degenerated and infiltrated with round cells and polymorphonuclear leukocytes to varying degrees. Beneath this was a more or less developed zone of granulation tissue, and, lastly, a zone of dense connective tissue from which capillaries passed into the zone of granulation tissue. The muscle bundles of the stomach, which were broken through in all but three instances, showed a varying degree of infiltration by round and plasma cells. The large vessels in the base of some penetrating ulcers showed closure by thrombus, or granulation tissue replacing the thrombus.

Two specimens of pyloric stenosis and two of hour-glass deformity showed active ulcers with no evidence of healing. The dense scar

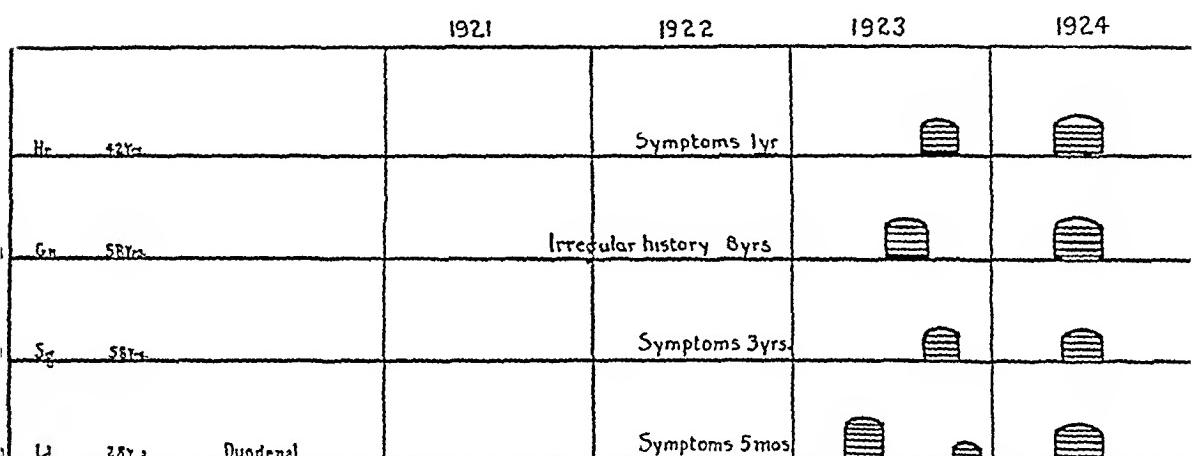


Fig 9—Course of cases of penetrating ulcer observed with repeated roentgenographic examinations

tissue forming the outer layer of the lesion represents a protective reaction of the organism but does not seem to aid repair of the ulcer itself. In fact, by pinching off the blood vessels and nerves it may conceivably interfere with repair.

In thirty-nine specimens of duodenal ulcer, however, eight showed convincing microscopic evidence of predominating reparative processes. While the active ulcers showed essentially the same lesions as the gastric specimens (although smaller in size and depth), these eight specimens showed no zones of exudate or necrosis. The defect in the mucous membrane, from 2 to 5 mm in diameter or in the form of a narrow, elongated, puckered slit, was formed by delicate granulation tissue, which seemed to arise from the stroma of superficial glands and often had a papillary arrangement. In two instances, a single layer of epithelial cells was found growing from the glands of the adjacent

mucosa downward into the defect and covering the delicate granulation tissue. Beneath the healing ulcer, denser connective tissue and muscle bundles were found drawn upward toward the surface. The Brunner's glands were seen on either side, but they seemed to play no part in the process of repair, having apparently been destroyed at the site of the ulcer during the active stage.

Two specimens of small duodenal ulcers with diverticulum formation showed necrosis still going on in the ulcer. Here, as in hour-glass deformity, the protective connective tissue contraction had not tended to actual healing.

ROENTGENOGRAPHIC EVIDENCE OF COURSE OF PEPTIC ULCER JUDGED BY DISAPPEARANCE OF NICHE

During the last two or three years, we have had the opportunity of observing the roentgenographic behavior of a small group of gastric and duodenal ulcers. From the large mass of hospital material, we have

Clinical Improvement and Diminution in Size of Niche in Cases of Peptic Ulcer

Age	Good, Niche Disappeared	Improved, Niche Smaller	Unimproved, Niche Unchanged	Recurrence of Symptoms and Niche
	From 20 to 40 years	3	1	1
From 40 to 60 years	7	1	6	2
Over 60 years	0	0	1	0
Duration of Symptoms	Niche Disappeared	Niche Smaller	Niche Unchanged	Recurrence of Niche
From 2 to 4 weeks	4	0	0	0
From 1 to 6 months	3	0	1	1
From 6 months to 2 years	0	0	3	0
From 2 to 10 years	4	0	5	1

chosen this group, because, small as it is, twenty in all up to date, each case has been continually under our clinical observation. In addition, we have had more than one roentgenographic examination during the attack, in the intermission period and, when the opportunity offered, at the onset of recurrent symptoms. In this way, we have been able to collect data and draw conclusions which can be compared with those deduced from the pathologic examination of resected specimens.

Occasional mistakes are undoubtedly made in which persistent peristaltic waves, overlying shadows of barium filled intestines, perigastric adhesions or localized spasms give a false impression of a penetration from within the viscera. In general, it may be said that the disappearance of a visible roentgenographic niche, as a sign of a penetrating ulcer, runs parallel with the clinical improvement in the course of the case, just as reappearance of the roentgen-ray evidence of the penetration occurs simultaneously with the recurrence of active symptoms.

Several competent observers have hesitated to accept the disappearance of the niche as a sign of healing in an ulcer Hollander⁶ reported a case in which the resected specimen showed an active ulcer though the niche was no longer present Many have warned against interpreting every projection in the contour of the stomach, as outlined with opaque meal, as a certain evidence of a penetrating ulceration One may allow for a percentage of error in the interpretation of the roentgenographic films, but the percentage is probably very small Repeated roentgen-ray examinations in the same case at various intervals go a great distance in automatically controlling such errors When one observes, in a fair number of cases, a definite parallelism between the clinical facts and the roentgen-ray evidence, one is sorely tempted to minimize theoretical objections and to consider the niche as a sign of ulcer and its disappearance as presumptive evidence of its healing

Whether the disappearing penetration means a fully healed ulcer, a scar, or merely a filling of its crater with granulation tissue as a temporary stage toward the healing process remains for future studies to disclose The thoroughness of the healing process, that is, the filling of the crater with new-formed connective tissue and the regeneration of the mucosa, undoubtedly depends on the length of the intermission period or the final permanency of the cure Until some one is fortunate enough to be able actually to show the stomach of an individual in which an observed niche has disappeared, there will always remain some healthy doubt as to the exact significance of the phenomenon The observation of this group of twenty cases with repeated roentgen-ray examinations has furnished the following data

1 The niche disappeared completely in ten cases (Figs 7, 8 and 9 and table), and partially in two additional instances In eight of the twenty cases, neither the niche nor the clinical symptoms were beneficially affected by the course of treatment

It may be that with a more persistent and more carefully supervised therapy the results would have been better The refractory patients had all been referred to the hospital wards and had received bed rest, alkalis and a modified form of Sippy treatment Ohnell⁷ reports a far larger percentage of success in such cases, and Buscher⁸ recently reported, in a series of 100 cases, seventy-one in which the niche completely disappeared, fifteen in which it diminished, eleven in which it remained unchanged, and three in which it disappeared only to reappear with the next attack of pain

⁶ Hollander, Edward Fallibility of Roentgenologic Evidence of Healed Gastric Ulcer, *J A M A* 80:29 (Jan 26) 1923

⁷ Ohnell Acta med Scandinav 53:706 (Jan) 1921

⁸ Buscher, J Arch f Verdauungskr 31:327 (July) 1923

Our own small series includes some patients with the most difficult examples of chronic callous ulcer, such as are known to haunt for years the wards and outpatient departments of large city institutions.

2 Of the cases in which the niche either disappeared or diminished, four patients were between the ages of 20 and 40 years and eight were between 40 and 60.

It is a significant fact that all the cases of failure to influence the size of the niche and prevent recurrence occurred in persons aged 45 or more. Most of them were between 50 and 60 years old.

3 We are impressed with the fact that the shorter the duration of the symptoms at the time that medical treatment was begun, the better the chance for healing. Thus, all our cases in which treatment was instituted within from two to four weeks of the onset of complaints, four in number, reacted favorably with disappearance of niche and symptoms. Of four patients complaining from one to six months, three completely cleared up and one showed a persistent niche.

On the other hand, the impression is gained that cases with long standing histories give less favorable results. Of the twelve patients complaining from six months to ten years or more, in only four did the penetration disappear. In one additional case, the ulcer presumably healed but broke down within a month, the niche reappearing. The remaining seven chronic patients were not influenced by treatment. Considering these twelve chronic cases as a subgroup, we note that three of the four favorable patients were less than 45 years of age, while of the eight unfavorable patients six were more than 45 years of age.

Again analyzing these long standing cases, we see that those with long intermissions between attacks heal more readily. On the other hand, in patients that have long continued, intermittent attacks, with short intervals of relief, the ulcer can occasionally heal, particularly when the patient is not advanced in years.

4 The clinical course of gastric ulcer is further well exemplified in the instances in which apparent cure was followed by a recurrence of symptoms and a reappearance of the niche. In one case (Case 8), the niche disappeared and complete relief from symptoms was observed for eighteen months. The patient returned to the clinic with recurring symptoms only slightly over one week in duration. An immediate roentgen-ray examination demonstrated the niche to be already present. Hematemesis shortly ensued. A thorough course of medical treatment resulted in cessation of all symptoms and again in the disappearance of the roentgenographic penetration. In a second case (Case 13), complete relief from symptoms for six months was followed by reappearance of the niche and of clinical symptoms. These patients were aged 50 and 58, respectively. In another case, a penetrating ulcer of the lesser curvature

disappeared under medical treatment, the patient feeling well for some months. A recurrence of symptoms for some days was followed by a sudden perforation of the same ulcer. A subtotal gastrectomy resulted in cure.

From a study of such cases, one is led to the conclusion that peptic ulcers probably heal under medical treatment, healing being more successful in younger persons and in those with a short clinical history. Healing also is possible in protracted cases in which the free intervals are long in duration and the attacks mild. If one assumes with Ohnell that forty and one-half days is the average length of time necessary for the disappearance of the niche and, hence, for healing, then all the cases in which the free interval is more than six weeks in duration have a greater predisposition and tendency to heal. Cases in which the symptoms are continuous or in which the intermission periods are less than six weeks, represent chronic callous, unhealing ulcerations.

Unfortunately, such physiologic healing is not always permanent, for reulceration may take place, and thus, as in Case 8 of this series, one sees exemplified the rather customary history of ulceration followed by disappearance of the niche, a long free interval and again ulceration, to be again followed by disappearance of the penetration. In both these cases, the niche reappeared at approximately the same point on the gastric wall as on the previous occasion, from which one might deduce that the so-called healed ulcer remains as a *locus minoris resistentiae*, evidencing a tendency to break down again and form a new ulcer in the same scar or in the granulating wound of the previous ulcer.

THE BEHAVIOR OF PEPTIC ULCER IN THE STOMACH WHICH HAS BEEN OPERATED ON

Those who are privileged to study and observe the behavior of peptic ulcer after operation will find in this opportunity a wealth of material which throws much light on the life cycle of ulcers. That ulcers can and do heal after simple gastro-enterostomy is amply demonstrated, not only by a fair percentage of clinical cures after such an operation but also by necropsy observations, made years after, of patients whose death has been due to some intercurrent disease. Surgeons who are forced to open the abdomen in such cases for secondary causes often find the scars of such healed ulcerations. Just what percentage of gastric or duodenal ulcers are cured by gastro-enterostomy remains today a much mooted question, the percentages reported by various surgeons ranging from 30 to more than 90 per cent. and depending to a great extent on the thoroughness with which the follow-up has been prosecuted and the open-mindedness or the bias of the critical observer. That gastro-enterostomy is a sure cure for all cases is, however, being

more and more questioned. The best example of the constitutional tendency continually to recreate ulcers in the same or in new situations in the gastric wall is to be seen in the cases of recurrence of the original ulcer months or years after gastro-enterostomy, and in that large and increasing problem of what to do for gastrojejunal and jejunal ulcers. It is not unlikely that most ulcers, particularly duodenal ulcers, heal at least partially after such an operation, for, in the largest percentage of cases, an interval of freedom from symptoms and apparent cure follows the surgical procedure. On the other hand, the not inconsiderable percentage in which this period is followed by one of recurrence of all the symptoms, including hemorrhage, bears mute witness to the fact that many such ulcers either heal incompletely or heal only to break down again in spite of the anastomosis. Years may elapse before the recurrent ulceration occurs, in one of our cases as long as six years intervened, but the tendency to recur is there nevertheless.

The recurrence of a lesser curvature ulcer after cautery or knife excision is another not infrequent manifestation of the constitutional tendency of an ulcer to reform in an imperfect scar. The impressive problem of the gastrojejunal ulcer looms larger daily. It is variably estimated that gastrojejunal ulcer occurs in from 2 to 16 per cent or more of all cases of gastro-enterostomy for ulcer. The high mortality in secondary operations for the relief of such secondary ulcerations makes this chapter of gastric surgery one demanding much serious attention, particularly from the point of view of preventing its occurrence.

The stories of some of the lamentable subjects of repeated surgical operations are very valuable when viewed from the angle of the life cycle of the ulcer and its underlying ulcer bearing constitution. One type of case is that in which, following a palliative gastro-enterostomy, the original gastric or duodenal ulcer heals but a new gastrojejunal ulcer forms. Another type of ulcer is that in which reperforation of the same ulcer has been noted years after the original operation. Still another group, though small, is that in which the original duodenal or gastric ulcer heals after gastro-enterostomy, but some time later operation is required for a chronic callous ulcer elsewhere in the gastric wall. Similar is the group in which, following the excision of a gastrojejunal ulcer, a second gastrojejunal ulcer forms. But the most interesting group from the standpoint of reulceration and healing is the following.

This group comprises three cases in which gastro-enterostomy had been performed for a gastric or a duodenal ulcer. Following this expedient, renewed symptoms required relaparotomy. At such a second operation, the original ulcer (lesser curvature of stomach or duodenum) was seen to be entirely healed, but a gastrojejunal ulcer had formed. In view

of the fact that the original ulcer had healed, the gastro-enterostomy was undone, and the original physiologic condition restored. Sometime subsequently, renewal of severe symptoms led to a third laparotomy, at which operation it was noted that in all three instances the primary ulceration had recurred, and in the identical site. In the case with the lesser curvature ulcer, it had recurred on the latter curvature and both duodenal cases showed renewed duodenal ulcerations. These examples are profoundly striking in that they show that, even though an ulcer is apparently well healed after a gastro-enterostomy, a return to normal conditions again brings into play the factors that had created and will again create the original ulcer.

Subtotal gastrectomy removes the ulcer bearing area of the mucosa of the stomach and the first portion of the duodenum, and leaves an anacidity permanently established in the remainder of the viscera. Since one cannot operate on the constitution of the patient, it would seem to be advisable, in the interest of the patient, to perform such a surgical procedure as will guarantee removal of not only that ulcer but also the milieu for the recurrence of a new one. This, subtotal gastrectomy seems to do.

SUMMARY

1 Chronic peptic ulcers may form within two or three weeks of the onset of symptoms. This conclusion is based on the history of the patient, the observation of the recurrence of a niche within two weeks of recurrence of the symptoms, and, finally, on the ease with which such short timed ulcers can be made to disappear under medical treatment (from ten days to two weeks).

2 Chronic ulcers achieve their maximum size within a few weeks and do not thereafter extend their borders.

3 Pathologic and roentgenographic evidence indicate that healing in the intermission stage does progress. The degree of healing and its permanency depends on various factors. The younger the individual and the shorter the history, the greater the tendency to healing. Cases with long intermission periods and with mild attacks heal more readily than those with continuous active symptoms. An ulcer in a person over 45 years of age can heal only with difficulty.

4 Histologic evidence indicates that healing takes place by the filling of the crater of the ulcer with firm granulation tissue, by retraction of the muscularis, by contracture of the opening and by regeneration of the mucous membrane. We have no pathologic specimen of gastric ulcer in which complete healing has taken place. We have several specimens indicating the healing of duodenal ulcers in the intermission stage.

5 Cases of duodenal ulceration in which there has been hemorrhage seem to heal most readily.

6 Neither pathologic evidence of healing nor roentgenographic demonstration of the disappearance of the niche is to be considered as proof of clinical cure. Ulcers may readily heal in the intermission stage but, unfortunately, show a tendency to break down again, probably at the same site. A certain number of ulcers eventually heal completely, others do not, and these become surgical cases.

7 The mishaps after gastro-enterostomy furnish many illustrations of the constitutional tendency of ulcers to reform in the same or in new sites of the stomach wall. Thus, recurrence *in situ* after local removal, recurrence of the original ulcer after apparent healing resulting from gastro-enterostomy (the large number of gastrojejunal ulcers) and, finally, the recurrence of the original healed ulcer when the gastro-enterostomy must, for some reason, be undone—all these point to the advisability of performing such an operation for ulcer as shall remove not only the ulcer but also the ulcer-bearing mucosa, namely, the operation of subtotal gastrectomy.

GASTRIC MOTOR ACTIVITY IN PATIENTS WITH PEPTIC ULCER[†]

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In any report of experimental work on chronic peptic ulcer, the method of arriving at a diagnosis of ulcer is important. I chose twenty-nine patients who presented (a) carefully elicited clinical histories of attacks of regularly recurring epigastric distress with definite relation to meal taking, (b) relief from pain by eating, by emptying the stomach and by alkalis (all of these repeatedly demonstrated during a ten or fourteen day period of hospital observation while on a diagnostic "test-out"),¹ and (c) complete relief from pain while on ulcer treatment. This lasted for four weeks in the hospital and continued for months at home (The follow-up on these patients extends over from one to two years in the Sippy routine.)

The above named conditions (a, b and c) were all characteristically present in the twenty-nine patients. In addition, (d) a number had gastric peristaltic waves and other evidence of chronic obstruction at the

* The work on twenty-nine patients reported here was begun at the suggestion and under the supervision of Dr B W Sippy, several years ago, when the writer was doing postgraduate study on the service of Dr Sippy in the Presbyterian Hospital of Chicago. The clinical material at my disposal during these years was abundant. Therefore, only such patients as were found peculiarly adaptable to the experimental work were selected for the study. Private cases, largely those of Drs B W and A F Sippy, were used.

1 In the Sippy routine of gastro-intestinal diagnosis, patients are subjected to rigid preliminary observation and study in the hospital. The distress that develops during this period of observation is carefully analyzed and shown to be consistent with the distress of ulcer before a diagnosis of ulcer is made. For example, it is actually determined that when the distress attributable to ulcer does appear, it comes on an appreciable time after eating an ordinary meal and not while eating or immediately after eating, but usually from one to three hours afterward. It is also determined that the distress is relieved in a characteristic manner by a small meal, consisting of two eggs, a cereal, two glasses of milk and some bread and butter, likewise, by the administration of adequate quantities of alkali or other chemical agents that have acid neutralizing properties. On other occasions when the distress is at its height, or when distress is present at a time when the stomach normally should be empty, a stomach tube is used to ascertain if food and gastric secretion, in quantity and quality compatible with a diagnosis of ulcer, are present in the stomach and if the emptying of the stomach gives characteristic relief to the pain. The painstaking accuracy with which a diagnosis of ulcer was made by Dr Sippy was recognized by all who observed his work, and can be surmised by those who read his scientific articles.

outlet, such as is obtained by finding a retention on motor meals, or sarcinae in stomach contents, (e) a number had blood in the stools which disappeared later on ulcer management, and some gave a history of hematemesis, (f) twenty-three of these patients showed unmistakable duodenal or gastric defects typical of ulcer by roentgen-ray examination, and nine of them were proved at operation. The rest showed suggestive roentgen-ray findings or were unsatisfactory because of poor visualization of the duodenum, due to its position.

Recently, reviewing the hospital charts of these patients, it seemed reasonable to believe that the diagnosis of peptic ulcer would remain unquestioned by medical and surgical clinicians versed in the diagnosis.

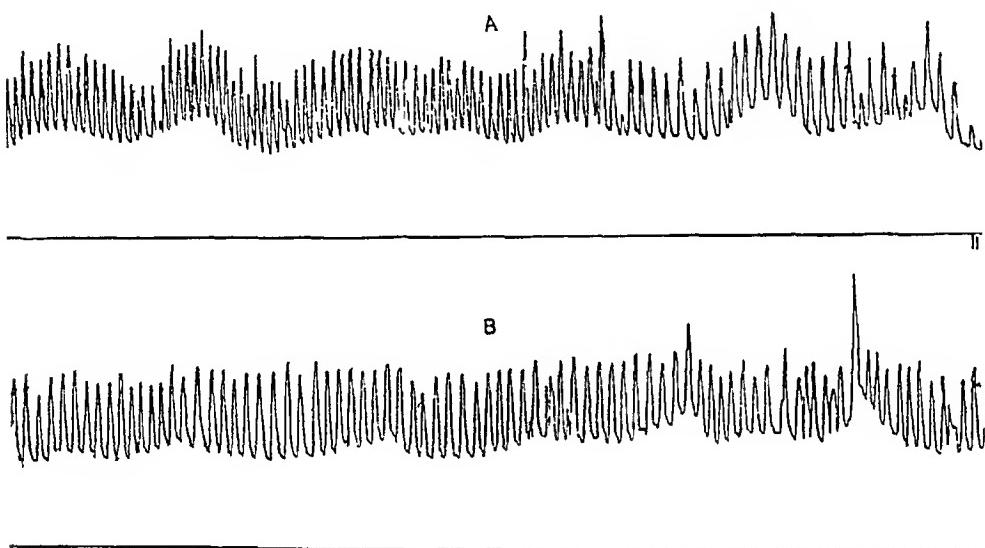


Fig 1 (Case 1).—A, peristalsis, during pain period, before alkali administration, at the two signals on base line, pain was momentarily aggravated, B, type of peristalsis, when pain had completely disappeared, following alkali administration.

of ulcer, because of the combination of signs and symptoms in the patients used for the work.

The investigation was conducted as follows. A patient previously diagnosed as suffering from peptic ulcer was studied during an attack of typical pain. At the onset of pain (as a rule from one to three hours after eating), the patient swallowed a small balloon, such as is ordinarily used to record gastric peristalsis in the method developed by Dr A. J. Carlson. Dr A. Luckhardt of the department of physiology at the University of Chicago gave helpful suggestions on the technical side of the investigation. The balloon is connected by means of rubber tubing to an air-bromoform manometer, which, through a rising and falling pointer, records intragastric changes in pressure on the smoked paper of a revolving drum (kymograph). Cardiac beats and the respi-

iations are superimposed on the gastric peristalsis by this method. The record of stomach peristalsis was continued for from one to one and one-half hours. Patients were asked to record any changes in pain, either increases or decreases, through an electric magnet. As a rule, the pain continued steadily or gradually increased, rarely decreasing in severity for over one-half hour. At that time, with the balloon in situ, patients were given by mouth chemical neutralizing agents in sufficient dosage to neutralize stomach acidity, usually from 30 to 60 grains (1.9 to 3.8 gm) each of sodium bicarbonate and calcium carbonate. The tracing was continued without artificial change of pressure in the balloon system (except in a few for accidental reasons) for thirty or forty minutes longer.

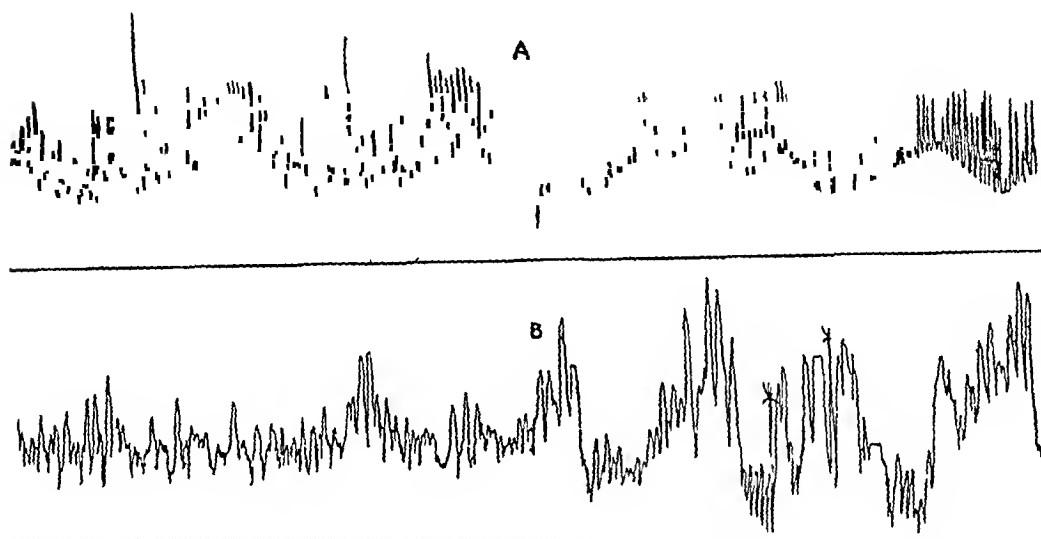


Fig. 2 (Case 2).—*A*, type of peristalsis, when pain was quite severe, before alkali administration, *B*, after alkali administration, when pain was gone.

It was originally planned to have patients swallow a Rehfuss tube as well as the balloon, simultaneously to check the acidity, but it was early demonstrated that the effort to swallow the balloon during an active pain period tended to make these patients vomit, so we abandoned the Rehfuss tube. Since we were primarily interested in the peristalsis, not in the acid figures, at from two or three to ten hour intervals following ordinary meals, we were content with knowing that all these patients had had high free acid findings on other occasions, as shown by Ewald, motor meals, and aspiration. At the end of the tracing, practically all the patients were aspirated. Usually the contents withdrawn contained food eaten at the previous meal, and the majority showed no free acid with dimethylaminobenzol, indicating that enough neutralizer had been given to control free acidity from the time of administration to the end of the tracing.

RESULTS

1 Of twenty-three tracings made during active distress periods, although the pain was invariably completely relieved after giving the neutralizer, (a) nine showed no change in peristalsis after the soda bicarbonate and calcium carbonate were given, (b) ten showed varying increase of peristaltic activity after the neutralizer, (c) three showed decreased peristalsis after the neutralizer, and (d) one showed decreased peristalsis for twelve minutes and then increased, beyond the prealkal period.

2 Of two tracings made during active distress periods in which the neutralizer did not relieve the pain completely, both showed no peristaltic change after the soda bicarbonate and calcium carbonate.

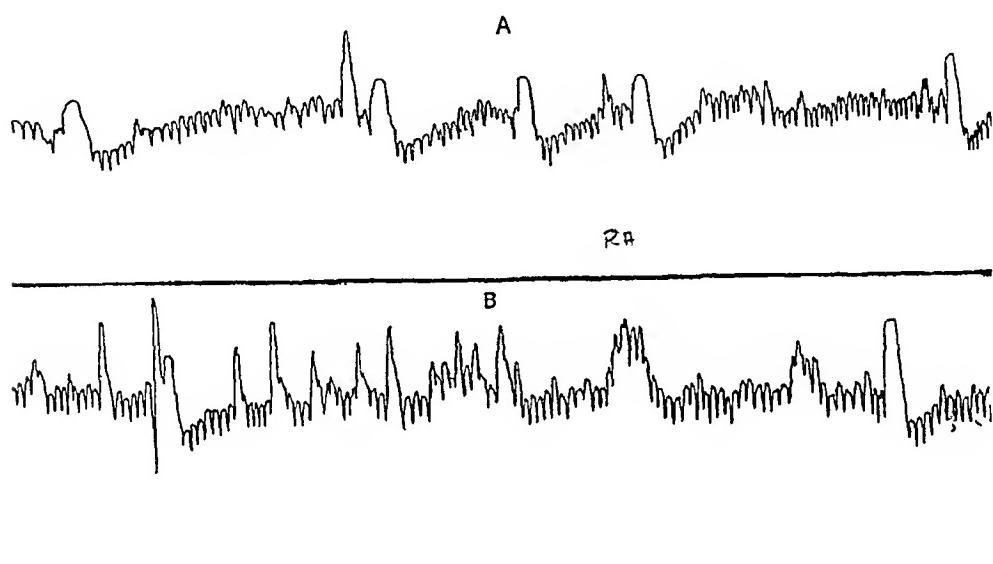


Fig 3 (Case 3) —A, peristalsis, when pain was present, before alkali administration (PA, pain momentarily aggravated), B, when pain was gone, after alkali administration.

The distention caused by the carbon dioxide gas, formed in quantities from the combination of hydrochloric acid with the large doses of neutralizer used, undoubtedly made it difficult for the patients to distinguish the last remnants of the typical ulcer distress from the discomfort caused by the distention. Without this overdistention of the stomach, Dr Sippy demonstrated that distress attributable to ulcer, unassociated with pain producing complications, such as perigastritis, is invariably completely relieved in from five to fifteen minutes by an adequate quantity of neutralizer. In the future, it is planned to give calcined magnesia, which liberates no carbon dioxide, together with smaller doses of carbonate in place of the large doses of soda bicarbonate and calcium carbonate used in these experiments.

3 Of four tracings taken during distress free periods in ulcer patients, two showed an increase of peristalsis following a neutralizer, the other two showed no change.

4 Nineteen showed no change in general tone following soda bicarbonate and calcium carbonate (as measured by the average distance of the tracing from the base line) In the remaining ten, there were artificial interruptions requiring small changes in the air-bromoform apparatus

CRITICISM

It is ideal to check the acidity and peristalsis simultaneously throughout the experiment This was not accomplished because human beings in pain make poorer experimental animals than pain free human beings, and untrained patients poorer experimental animals than trained laboratory workers, man or dog

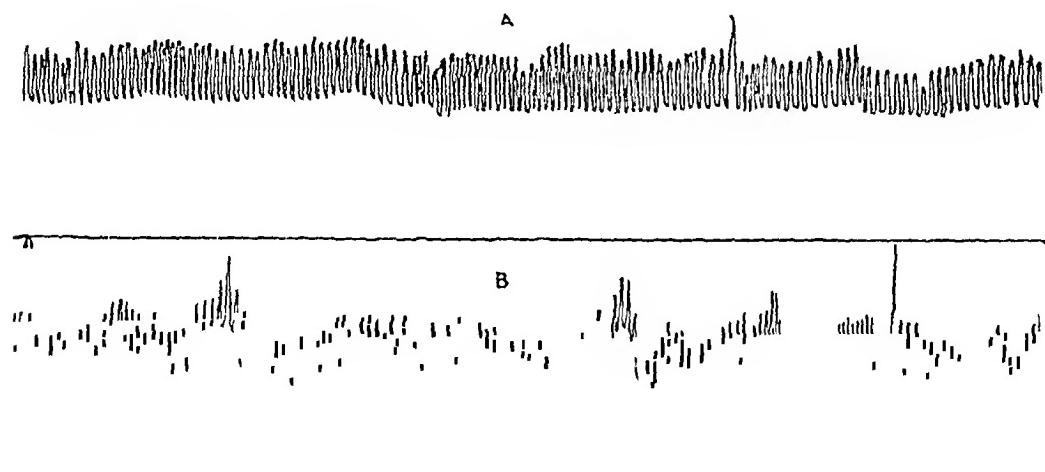


Fig 4 (Case 4)—*A*, peristalsis, when pain was severe, before alkali administration, *B*, when pain was gone, after alkali administration When the acid findings were concomitant, the peristalsis showed (*a*) a moderate but definite increase after alkali, and (*b*) no relation to severity, mildness or absence of distress Free acid was highest when the pain was severest, lower when the pain was mild, and absent when the pain was gone The findings were 6 43 p m, severe pain, very low tonus, free hydrochloric acid 95, 6 52 p m, pain mild, long tonus waves, free hydrochloric acid 44, 7 03 p m, pain mild, long tonus wave, free hydrochloric acid 50, 7 10 p m, pain gone, second type peristalsis, free hydrochloric acid 0, 7 43 p m, pain absent, low tonus wave, and free hydrochloric acid 0

The balloon in the fundus method does not record the entire peristaltic cycle Reynolds and McClure of the Peter Bent Brigham Hospital, in 1922, stated that "the balloon method does not accurately record fluoroscopic observations" This method cannot record all that is going on in the stomach, such as double or triple peristaltic contractions, or local or pyloric spasms It is admitted that it records changes of pressure in the fundus Indeed, it records very delicate changes in pressure in the fundus, as is shown by its record of the heart beats against it Prepyloric contractions may not cause changes of pressure in the fundus sufficient to register through the balloon, but it seems

probable that they do. It is likewise difficult to see how any peristaltic wave traversing the antrum would fail to register on the balloon.

Lastly, we must be careful in drawing conclusions as to the actual factor responsible for the varying changes in gastric peristalsis which were observed in sixteen of the twenty-nine patients following soda bicarbonate and calcium carbonate. Changes in types of peristalsis during digestion may occur in normal and abnormal human beings at varying times when short records, such as these, are taken.

COMMENT ON MAIN THEORIES OF CAUSE OF PAIN IN PEPTIC ULCER

Before drawing conclusions from this series of tracings, it may be profitable to review briefly the chief theories of the cause of pain in peptic ulcer.

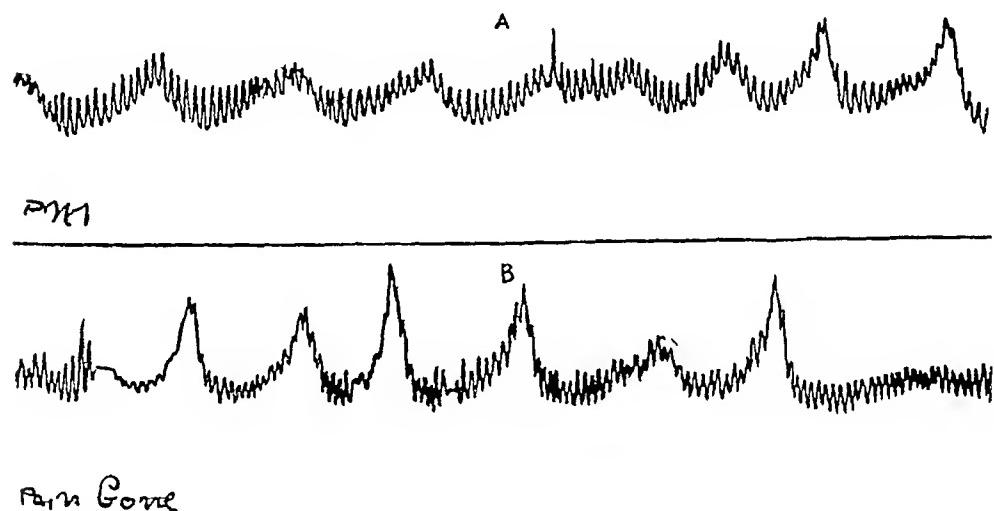


Fig. 5 (Case 5).—A, peristalsis, when pain was present, before alkali administration, B, when pain was absent, after alkali administration.

One conceives that the free hydrochloric acid has something to do with the pain when the ulcer is in an "irritable" state. This idea is founded on the universal observation that when the hydrochloric acid is reduced or completely neutralized by alkalis or food, or removed by emptying the stomach of food and secretion, the pain of uncomplicated ulcer disappears. The foregoing experiment neither proves nor disproves this theory.

Carlson, Ginsberg, Tampowski, Hamburger and Hardt have claimed that active peristalsis is responsible for the pain and that the alkali, by affecting peristalsis, gives relief of pain in ulcer. They have attempted to prove this by taking tracings on ulcer patients while the pain of ulcer is present and at other times when it is not present.

Drawing conclusions from his tracings, Carlson thought that the peristaltic contractions were felt as *pain* when the ulcer is in an "irritable state," while similar peristalsis might go on without conscious sensations at other times when the tissues were less irritable. His work was done on stomachs that were being aspirated at intervals through a Rehfuss tube, so that they contained no food and, at times, very small amounts of secretion.

Hardt believed that by demonstrating more active types of peristalsis during the pain periods in a few patients, he had proved that the peristalsis was the cause of the pain. Then Carlson, who had shown that many things, such as water, acid and alkalis, put into the stomach temporarily inhibited peristalsis, concluded by indirect reasoning that alkali stopped the pain of ulcer by inhibiting peristalsis. Not one of them has ever given quantities of alkali adequate to neutralize the free hydrochloric acid during an ulcer distress period when food and secretion were present in the stomach and noted the effect on peristalsis, as the writer has done. Only four of the twenty-nine patients reported in this study showed decreased peristalsis after the neutralizer, a result in no way justifying the theory of the foregoing workers.

Carlson has thought that "tonus," even of normal variety, is felt as pain when an ulcer is in the "irritable state." Why a neutralizer like calcined magnesia should allay this irritability in so perfect a fashion as it does and magnesium sulphate, which does not combine with hydrochloric acid, should not (both, in addition, being decided stimulants to the intestine) is a known fact difficult to reconcile with Carlson's interpretations.

Hamburger and Ginsberg have suggested that increase of tone is responsible for the pain and that alkali changes tone, but have offered no direct proof. This experiment shows that there is regularly no change of tone after the administration of soda bicarbonate and calcium carbonate.

Another theory is that localized spasm at the site of the ulcer is responsible for the pain of ulcer. No direct proof for this conception is at hand.

Spasm at the pylorus or first portion of the duodenum with "intensified tonus usually" is conceived to be responsible for the pain by the above mentioned workers, but again the proof, even a method for proof, is lacking. In roentgenographic observation, although hyperperistalsis, reverse peristalsis and irregular peristalsis are easily observed, it is very difficult to demonstrate pylorospasm, according to Reynolds and McClure, who reported a very thorough piece of radiographic work on

sixteen ulcer patients.² Pylorospasm, according to them, is always intermittent. They concluded that motor disturbances of the stomach or pyloric region are almost invariably associated with ulcer pain. In some of these cases, however, the peristalsis remained unchanged after the pain stopped or changed to abnormal type. There was, in other words, no such unfailing correspondence in change of peristalsis, during pain free periods, as there is unfailing relief of pain, when sufficient neutralizer is administered to an ulcer patient.

Any theory of motor phenomena as the cause of pain in ulcer, except that of continuous localized spasm, is at variance with the clinical observation that the distress of ulcer, when present, is usually continuous. The

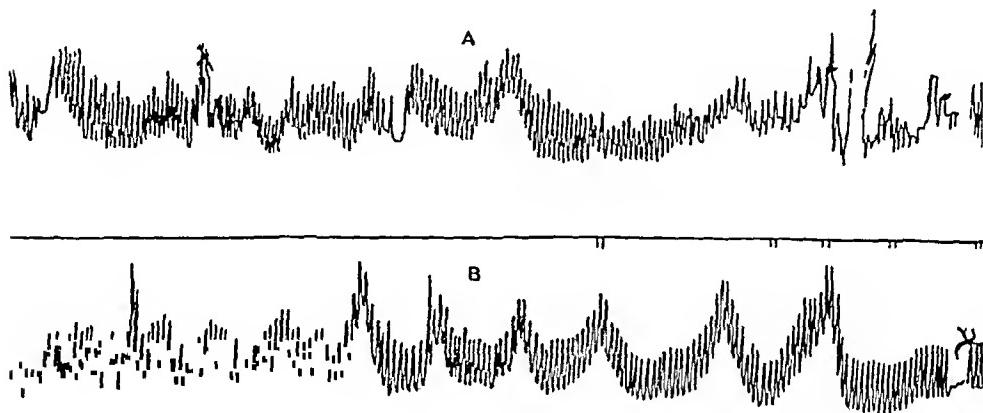


Fig 6 (Case 6).—A, peristalsis, when pain was severe (the patient groaning) before alkali administration, signals on base line indicate that pain was especially aggravated at these points; B, peristalsis, when pain was entirely relieved, after alkali administration.

patient himself often describes his pain as gnawing or boring, not as a "spasm." That patients with peptic ulcer, during their severest pain periods particularly, have exacerbations of pain superimposed on the less acute but continuous distress is well known, however. One can conceive that these exacerbations might fit in with the periodicity of the peristaltic contractions. Hardt has shown tracings in which the patient signaled his greatest distress each time that the kymographic pointer approached the summit of a wave. In the tracings reported here, the patients were quite regularly unaware of these exacerbations at the height of the wave curve. In one tracing, there seemed to be fair

² Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch. Int. Med. 29:1 (Jan.) 1922.

correspondence between the wave and exacerbations of pain. In another, in which probably the highest waves of any obtained were recorded, there was some correspondence, but there also were shown aggravations of pain without accompanying waves and vice versa. In still a third patient with very active peristalsis, the waves themselves were felt as a "turning over" sensation in the abdomen even after the neutralizer was given and pain stopped, but the pain itself had no definite relation to the peristalsis at any time during the tracing.

It has always been difficult to explain the quick, unfailing relief to the pain of peptic ulcer obtained by giving a sufficient quantity of neutralizer, by emptying the stomach or by eating on the basis of motor activity alone. It would seem that a similar quick change in motor

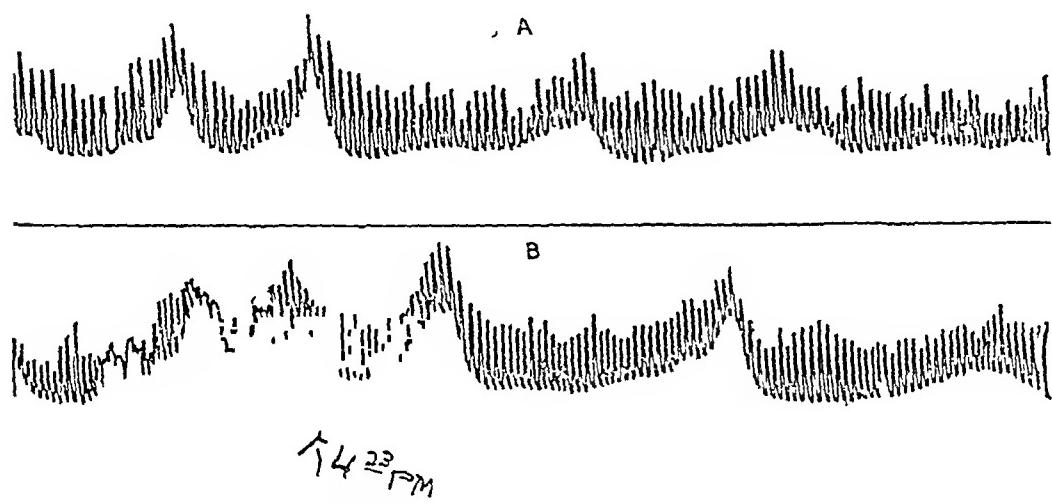


Fig. 7.—*A*, peristalsis before alkali administration, *B*, after alkali administration, no pain throughout.

phenomena should be demonstrable. It also is difficult to conceive how soda bicarbonate, calcium carbonate or calcined magnesia could depress localized spasm so completely and quickly, without affecting general motor activity as well, though it is conceivable that they might in this way relieve ulcer pain, if local spasm were the cause.

CONCLUSIONS

In this series of experiments there is no evidence that soda bicarbonate and calcium carbonate relieve the pain of ulcer through lowering tension or tone or through decreasing peristalsis of the stomach, so far as either of these factors can be recorded by the method used.

The fact that, in ten of the twenty-three tracings, varying increases of peristalsis were recorded, and in four, only decreases following the neutralizer is not of sufficient significance in so small a number of tracings as to rule out the factor of the possible coincidence of peristaltic

changes that may occur in the progress of digestion in ulcer patients If one attached significance to the increase in peristalsis following alkali shown in ten, one would again need to explain the absence of any change in nearly as great a number (nine)

Carlson has shown that peristaltic activity of the stomach is present when food and secretion are in the stomach, but that it is most active in the fasting stomach Dr Sippy showed, in innumerable hospital tests, that the pain of uncomplicated ulcer is present only when gastric content in adequate quantity and quality is present in the stomach In the opinion of the writer, the pain and the peristalsis are probably coincidental

The foregoing experiments do not bear out the theory that the peristalsis causes the pain There probably are a number of responsible factors, none of them as yet definitely proved or known

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NONSPECIFIC ULCERATIVE COLITIS *

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Introduction and definition of terms

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INTRODUCTION AND DEFINITION OF TERMS

The subject of ulcerative colitis of unknown etiology has received comparatively little attention since the condition was first described by Wilks¹ and White². Its prevalence and rapid spread in asylums in

* These investigations were made possible through the liberality of Mr W D Thornton in establishing the Thornton Research Fund. All the cases described are taken from the service of Dr Jerome M Lynch at St Bartholomew's Hospital.

1 Wilks, S., and Moxon, W. Lectures on Pathological Anatomy, Ed 2, 1875, p 408

2 White, W H. On Simple Ulcerative Colitis and Other Rare Intestinal Ulcers, Guy's Hosp Rep 45 131, 1888

England at that time, particularly in those for the insane, was made the subject of investigation by a special medical commission. In a review of these accounts, one cannot help thinking that many cases of asylum dysentery described in the early English reports were really bacillary or amebic dysentery.³ In 1902, Vedder and Duval⁴ proved that epidemics of dysentery occurring in American institutions were caused by *Bacillus dysenteriae*. Moreover, in 1904, Eyre⁵ proved that the epidemics occurring in English institutions were caused by *Bacillus dysenteriae*. Between the years 1901 and 1904, 1,155 cases occurred in the London county asylums, 266 of them being fatal. Yet in spite of stringent attempts at isolation and disinfection, there was no diminution in the incidence of the disease.⁶ The difficulty of isolating *Bacillus dysenteriae*, except at the onset of acute cases of bacillary dysentery, because of the rapidity with which this organism is outnumbered by *Bacillus coli*, makes it seem quite likely that a great many cases of ulcerative colitis might commence as a specific infection but rapidly pass over to a non-specific type. Knobel, Ackland, Targett⁷ and others suggested that the condition might be a trophic neurosis associated with disease of the nervous system. The strong resemblance of symptoms and lesions with absence of any etiologic factors, in the English cases, lead us to conclude that the majority, if not all, of them could be classified under nonspecific ulcerative colitis. The distinct separation of this type from bacillary dysentery was recognized by such eminent observers as Osler and Allchin.

The terms "asylum dysentery," "idiopathic ulcerative colitis," "innominate ulcerative colitis," "simple ulcerative colitis" and "ulcerative colitis" have been used to describe what is apparently one and the same condition. Because of the lack of evidence pointing to the presence of a definite etiologic factor, Lynch has applied the name of "nonspecific ulcerative colitis" to this group of cases. Our acceptance of this title will, of necessity, bar consideration of ulcerative conditions of the colon having any of the following etiologic bases:

1 Constitutional disease—Bright's disease, gout, pneumonia, lead poisoning and cardiac disease

3 Gemmel, J F. Idiopathic Ulcerative Colitis, 1898.

4 Vedder, E B., and Duval, C W. The Etiology of Acute Dysentery in the United States, J Exper Med 6: 181-205, 1902.

5 Eyre, J W H. Asylum Dysentery in Relation to B Dysenteriae, Brit M J 1: 1002-1004, 1904.

6 White, W H., cited by Albutt and Rolleston. System of Medicine (Diseases of the Colon) 3: 826-840, 1907.

7 Quoted from Tuttle, J P. Diseases of the Anus, Rectum and Pelvic Colon, 1906 pp 180-183.

2 Specific bacterial or protozoal ulcerative conditions—typhoid, ameba histolytica dysentery, bacillary dysentery, tuberculosis and syphilis

3 Malignant disease

4 Trophic disturbances due to interference in the nerve supply of the colon

5 Mechanical trauma—hard feces and foreign bodies

6 Vascular changes—embolism of the superior mesenteric artery and cirrhosis of the liver

GROSS AND MICROSCOPIC ANATOMY OF THE COLON

Gross Anatomy—In man, the colon starts in the right iliac region as a dilated pouch, the cecum, into which the small intestine opens, passing the ileocecal valve. From the cecum, the colon passes up toward the liver, then transversely across the upper part of the abdominal cavity to the spleen and finally downward to join the rectum at the rectosigmoidal sphincter. The average length of the colon is 22 inches (55.5 cm). The cecum and ascending colon are usually only partly covered by peritoneum, while the remainder of the colon possesses a mesentery. The sigmoid flexure or pelvic colon is the narrowest portion of the colon and is mobile by reason of its long mesentery. Commencing at the base of the appendix and surrounding it is a layer of longitudinal muscular fibers which, as it passes upward on the colon, forms three flat longitudinal bands, each being about 12 mm in width. These bands are about one-sixth shorter than the intestine proper and thus cause sacculation of the colon. The mucous membrane of the colon is smooth and raised into folds corresponding to the spaces between the sacci.

The arterial supply of the colon is derived from the superior and inferior mesenteric branches of the descending aorta, the former supplying the cecum, ascending and right part of the transverse colon, the latter supplying the remainder of the transverse and all of the descending colon, sigmoid flexure and part of the rectum. The arterial branches in the wall of the colon do not freely anastomose. Free anastomoses usually occur by a series of loops which lie close to the mesenteric borders of the colon. In the sigmoid flexure, the anastomoses usually occur nearer the base of the mesocolon. The superior mesenteric vein follows the general course of the artery and unites with the splenic vein behind the neck of the pancreas to form the portal vein. The inferior mesenteric vein begins as the superior hemorrhoidal of the rectum and usually empties into the splenic vein.

The lymphatic supply of the colon follows the course of the blood vessels. According to Jamieson and Dobson,⁸ the lymph nodes can be divided into the following groups:

1. The epiploic nodes, which lie on the intestinal wall and in the appendixes epiploicae, being especially numerous in the pelvic colon. These drain into Groups 2 and 3.

2. The paracolic nodes, which lie along the mesenteric border of the colon.

3. The intermediate groups, which lie along the arteries.

4. The main groups—middle colic, lying on the middle colic artery, and left colic, lying on the left colic artery near its origin and on the terminal portion of the mesenteric vein. These nodes drain into the superior mesenteric, celiac and lumbar nodes. The inferior mesenteric group lies on the artery and drains into the lumbar glands which drain the pelvic colon.

Some of the lymphatics of the left portion of the transverse colon drain into the nodes at the hilum of the spleen through the gastrocolic omentum.

The nerve supply to the colon is derived from the sympathetic plexuses around the branches of the superior and inferior mesenteric arteries.

Microscopic Anatomy.—The colon consists of four coats:

1. Mucosa, made up of a simple columnar epithelium with goblet cells resting on a basement membrane, beneath which is the tunica propria containing capillaries and diffuse lymphoid tissue. Externally is the muscularis mucosae. The glands are of the simple tubular type.

2. Submucosa, containing solitary follicles.

3. Muscularis, consisting of an internal circular layer (especially thick in the intervals between the sacculi and forming the internal sphincter of the anus) and an outer longitudinal layer forming the bands, or taeniae, above described.

4. Serosa, derived from peritoneum, covering the sigmoid and cecum completely, the ascending and descending colon in front and at the sides and the transverse colon almost completely.

PHYSIOLOGY OF THE COLON

Hertz⁹ finds that, in man, it requires about two hours for food to pass from the ileocecal valve to the hepatic flexure, and about four and

⁸ Quoted from Mummery, P. L. Diseases of the Colon, 1910, pp. 7-8.

⁹ Hertz, A. H. The Passage of Food Along the Human Alimentary Canal, Guy's Hosp. Rep. 61: 389-427, 1907.

a half hours to reach the splenic flexure. From this point, the food material advances very slowly toward the rectum. It requires from sixteen to seventeen hours for food to pass from the splenic flexure to the lower end of the sigmoid, and six hours to pass through the sigmoid, as compared with four and three-eighths hours for movement through the 20 feet (50 cm) of small intestine. Cannon¹⁰ divides the large intestine into two parts. In the first corresponding to the cecum, ascending and transverse colon, the most frequent movement is antiperistalsis. The fluid or semifluid material is forced back toward the small intestine, the entrance to which, however, is guarded by the ileocecal valve. The object of this delay is primarily for the absorption of

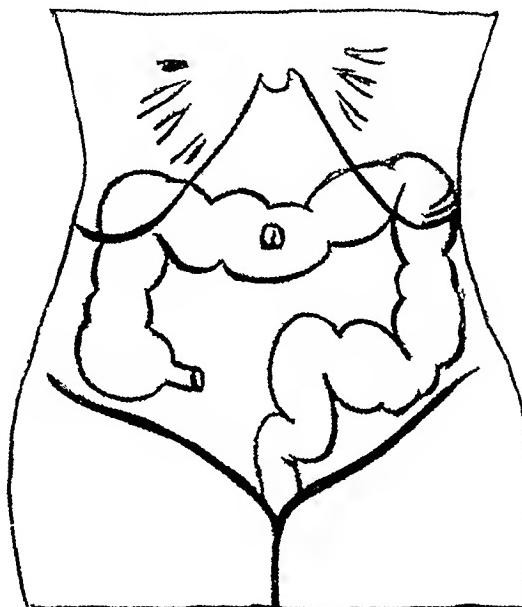


Fig 1.—Projection of outline of colon on abdominal parietes

water and secondarily to complete the process of digestion. The importance of fluid absorption is evident from the phenomenon of intense thirst displayed by patients having a right inguinal colotomy. According to Keith and Mummery, the cecum bears the same relationship to the large intestine as the stomach bears to the small intestine. In some of the lower animals, the cecum is actually the main organ of digestion. In the second portion—the descending colon—the food material, which is now quite solid, is moved on by peristaltic waves toward the rectum.

The motor nerve fibers leave the cord in the second to fourth sacral nerves, and reach the colon through the hypogastric plexus. The inhibitory fibers probably leave the cord in the lumbar nerves and reach the colon through the sympathetic chain and inferior mesenteric ganglions. The type of movement in the colon is generally held to be

¹⁰ Cannon, W. B. The Movements of the Intestines Studied by Means of the Roentgen Rays, Am J Physiol 6 251, 1902

the same as in the small intestine, except for the relative infrequency in the former a local rhythmical constriction and a progressive peristaltic movement. According to Hertz,⁹ fecal material is normally absent from the rectum except just before defecation. The sigmoid flexure acts as the normal fecal reservoir. The feces are retained in the rectum by the tonicity of the internal and external sphincters, the latter being in greater tone than the former. With distention of the rectum by the feces, there arises the normal stimulus to defecate, which act is effected by peristaltic action of the colon and rectum, occurring simultaneously with relaxation of the sphincters and fixation of the diaphragm.

It is interesting to note that the normal mucous membrane of the colon does not possess ordinary tactile or pain sensation. The latter is

TABLE 1.—*Comparative Figures of Frequency of Nonspecific Ulcerative Colitis*

Hospital	Period	Years	Number of Cases
St Bartholomew's Hospital, New York City	1920-1923	approximately, 3	41
Guy's Hospital, England	1888-1907	20	50
London Hospital, England	1894-1908	15	22*
Royal Free Hospital, England	1883-1907	25	2
St Bartholomew's Hospital, England			24
St George's Hospital, England	1883-1906	23	19
St Mary's Hospital, England	1884-1907	23	19
St Thomas' Hospital, England	1883-1908	25½	80
University College Hospital, England	1883-1908	25	38
Westminster Hospital, England	1884-1908	25	42

* Based on postmortem reports.

also absent from the visceral peritoneum. The parietal peritoneum and the mesentery of the colon, however, do possess pain sensation. The mucous membranes of the lower part of the rectum also possess definite pain sensation. Violent peristalsis will also produce pain due to muscular contraction of the intestine.

CLINICAL ASPECTS OF NONSPECIFIC ULCERATIVE COLITIS

Incidence.—During the period of thirty-four months (December, 1920, to October, 1923), our records show a total number of forty-one cases of nonspecific ulcerative colitis (combining the private records of Dr Jerome M Lynch and those of St Bartholomew's Hospital).

Table 1 gives a comparison of our figures with those of other institutions. As stated above, the English figures probably include some cases of bacillary dysentery, but, because of the incomplete or doubtful bacteriologic data, they could not be excluded.

The relatively greater frequency shown by our figures is probably due not to any increase in the incidence of nonspecific ulcerative colitis, but, rather, to greater care in recognition of the disease.

Age—The age at the time of onset of symptoms, in our series, is shown in Table 2

Analysis of the figures in Table 2 shows the greatest incidence (70 per cent) between the ages of 20 and 40 years, as summarized in Table 3

Our figures correspond to those reported by other institutions, e.g., Guy's Hospital, average age, 35.8, London Hospital, 37, St Bartholomew's Hospital, 39.2, St Thomas' Hospital, 70 per cent between 20 and 45 years, University College Hospital, forty out of fifty-one patients

TABLE 2—*Age Incidence of Nonspecific Ulcerative Colitis in Forty-One Cases*

Case Number	Age, Years	Case Number	Age, Years
1	31	22	15
2	29	23	25
3	24	24	34
4	40	25	45
5	30	26	27
6	61	27	17
7	27	28	35
8	36	29	52
9	33	30	21 months
10	29	31	36
11	26	32	50
12	23	33	43
13	30	34	29
14	32	35	24
15	34	36	50
16	18	37	28
17	29	38	60
18	32	39	41
19	35	40	23
20	43	41	34
21	22		

TABLE 3—*Summary of Age Incidence*

Age	Number of Cases
Less than 20 years	4
From 20 to 29 years	16
From 30 to 40 years	12
From 40 to 50 years	6
Over 50 years	3

between 20 and 40 years, Westminster Hospital, thirty-one out of forty-two patients between 20 and 40 years

Sex—In our series, sex incidence was as follows: male, nineteen, female, twenty-two, the single women numbering eight and the married fourteen

It will be seen that both sexes were affected about equally, and married women more than single women

Mortality—Five of our patients died. Patient 20 of pneumonia, Patient 22 of acute infection of the small intestine, Patient 27 of acute dilatation of the stomach following ileostomy; Patient 41 of perforation of the cecum with general peritonitis, Patient 8 of postoperative vol-

vulus of the small intestine. Of course, a short follow-up period of three years would not justify one in drawing any conclusions from these figures, especially because of the susceptibility of these patients to reinfection from time to time.

Residence—We have been able to elicit no evidence pointing to an infection (bacterial or protozoal), endemic or epidemic. Almost all our patients came from localities in which hygienic conditions were good, and none traveled to any extent.

Family History—No patient gave a history of similar disease in any other member of the family.

Occupation—The great variety of occupations in which these patients were engaged makes this source of origin of the disease seem quite unlikely. Most of the patients had more or less sedentary occupations not requiring extensive contact with persons or with poisonous materials.

TABLE 4.—*Incidence of Previous Illness Having Possible Etiologic Relationship*

Associated with, or possibly following operation for fistula (Cases 5 and 35)	2
Indiscretion in diet, especially sugar or milk (Case 6)	1
Constipation (Cases 11, 19, 1 and 4)	4
Nervous shock (Case 12)	1
Following operation for hemorrhoids (Cases 13 and 14)	2
Following operation for appendicitis (Case 17)	1
Following operation for ovarian tumor (Case 9)	1
Following attack of acute colitis (Case 20)	1
Associated with ulcerative condition of mouth and purulent eruptions on skin (Case 27)	1
Hyperthyroidism (Case 33)	1
Influenza (Case 34)	1
Associated with attacks of indigestion (Cases 38 and 39)	2

In the remaining twenty-three cases, the patients could not definitely associate the onset of the disease with any other condition. They were apparently quite well. It is interesting to note that six of the eighteen cases in Table 4 followed operations, and four of these were on the rectum. "Indiscretion in diet" (Case 6) might be included under "attacks of indigestion" (Cases 38 and 39) possibly causing ulcerative colitis through the local irritating action of ingested food or in the process of elimination of metabolic food poisons through the wall of the colon. Severe constipation is undoubtedly a factor, in that hard fecal masses may mechanically injure the wall of the colon. The nervous influences at play in hyperthyroidism and "nervous shock" may possibly exert their effects by means of the excessive peristalsis and diarrhea often associated with these conditions. Case 27 is very interesting in that this patient seemed to have a susceptibility to ulcerative conditions all over the body. He eventually died with involvement of the small intestine. This patient corresponds to the type described by

Tuttle as the anemic, broken down person suffering from some other form of disease or exhausting condition

Mummery¹¹ cites a case of nonspecific colitis which started as an acute specific dysentery. The protozoal agent, however, soon disappeared, and only *Bacillus coli* or streptococci could be demonstrated as possible etiologic agents. Similar observations have been made by Lynch¹².

Yeomans¹³ describes a series of sixty-five cases, thirty-seven of which had no etiologic basis. Of the remainder, five gave a history of amebiasis, six of dietary indiscretion, five of severe constipation and three of exposure.

TABLE 5.—Duration of Symptoms in Thirty-Five Cases Before Coming Under Observation

Case	Duration	Case	Duration
1	5 years	20	1 year
2	9 years	22	2 years
3	2 years	23	2 years
4	2 weeks	25	5 weeks
5	4 years	26	1 year
6	15 years	27	2 years
7	8 months	28	1 month
8	14 months	29	2 years
9	20 years	30	8 months
10	2½ years	31	6 months
11	2 years	33	18 months
12	10 months	34	18 months
14	10 years	35	4 years
15	3 weeks	38	18 months
16	9 months	39	10 years
17	2 years	40	1 year
18	1 year	41	5 weeks
19	4 years		

Mode of Onset.—Of those cases giving a definite time of onset, twenty-one were gradual and seventeen acute. The first symptoms or signs noticed by the patients were as follows: bloody stool in seven cases, diarrhea and bloody stool in seven cases, abdominal pain, six cases, abdominal pain and diarrhea, four, abdominal pain and bloody stool, three, mucus and blood in stool, three, pus and blood in stool, two, diarrhea, two, and constipation alternating with diarrhea in one case.

It will be noted that most of the cases were of rather long duration, indicating that the infection, if present at all, must have been subacute. In fact, the cases which came under our observation early were all severe.

11 Mummery, P. L. The Operative Treatment of Ulcerative Colitis, Brit. M. J. 1:497 (April 10) 1920.

12 Lynch, J. M. Diseases of the Rectum and Colon, 1914, p. 334.

13 Yeomans, F. C. Chronic Ulcerative Colitis, J. A. M. A. 77:2043 (Dec 24) 1921.

Clinical Picture—The acute cases often begin with severe diarrhea and colicky or gripping pain, usually referred to the front of the abdomen. As a rule, however, the onset is gradual, with passage of blood and mucus in the stool. The abdominal pain, if severe at first, may entirely disappear in a short time, only to recur after a period varying from several minutes to hours. Relief is usually obtained by movement of the bowels, especially if accompanied by passage of flatus. Tenesmus may be present if the rectum is involved. The passage of blood, mucus and pus by rectum is characteristic of ulcerative colitis. According to Hurst,¹⁴ when the pelvic colon and rectum alone are involved, the stools may be solid. In other cases, diarrhea alternates "with constipation. Often a patient will complain of frequency and urgency, but does not feel satisfied at stool. There still remains a more or less constant desire to defecate. In many cases, vomiting is a troublesome symptom, in others, frequency of micturition is evident. The constant loss of blood, accompanied by passage of great quantities of water and undigested food in the diarrheal stools, soon leads to loss in weight, anemia, anorexia and marked weakness. In many cases, the patient is bedridden sallow in appearance and often desperately ill. There is an accompanying hyperpyrexia, usually not very high, varying around 100-102 F., by rectum, except when a complication exists. Death usually occurs from exhaustion.

The foregoing description applies to an average fairly acute case. All sorts of variations occur. Some of our patients, while under observation in the hospital, ran no fever at all. Some have only two or three bowel movements a day. Loss of weight is a very constant feature, one patient (Case 18) losing 35 pounds (15.9 kg.) within one year. In many patients, one may feel what is often described as a "thickening" of the cecum and sigmoid, probably due to a hypertonic state of the muscular coat. Pressure on the sigmoid will often produce a desire to defecate.

ANALYSIS OF SPECIAL SYMPTOMS AND SIGNS

Diarrhea—This symptom, while usually occurring early, ensues quite regularly sooner or later in all cases showing ulcerating lesions anywhere above the rectum. It is probably due to excessive peristalsis, which is, in turn, brought about by the irritating effect of intestinal contents on the exposed nerves of open ulcers. Mummery found that a traumatic stimulus to the intestinal mucosa, such as nipping it with the end of a pair of forceps, always resulted in a marked peristaltic contraction, which was always local. The diarrhea may vary from a

few stools each day to twenty or more. The largest number of stools are passed usually in the morning, and the first movement may be almost solid. One or more bowel movements occur after each meal. When the pelvic colon and rectum alone are involved, the stools may be solid. In a number of our cases, constipation alternating with diarrhea was the rule (Cases 28 and 30). Sometimes there is a long history of slight bowel irregularity, with occasional passage of mucus and blood. One patient (Case 35) was constipated throughout his illness.

Character of Stools.—The stools are most often fluid, dark brown and foul. When accompanied with blood, the latter is usually also fluid and bright red, indicating its recent origin. Some patients note the presence of blood, especially after a period of constipation. We have often noted that the bloody stool may occur independently of the diarrheal condition. The blood is not thoroughly mixed with the stool, and, when the latter contains much fluid and only some fecal material, the solid particles may be specked with blood. Occasionally, small or large recently detached clots may be passed. The mucus may be clear or turbid from admixture of pus. Hale White describes the occasional presence of shreddy sloughs, which, under the microscope, appear to be quite structureless and show an occasional epithelial cell or leukocyte.

Examination of the feces shows that the food material has been fairly well digested, except in cases in which the ileum is involved. Here much undigested starch and protein (meat fibers) are present, the stools are offensive, and a great deal of flatus is passed.¹⁵ The feces are usually alkaline in reaction except when a great deal of carbohydrate fermentation has occurred.

Abdominal Pain.—Most of our patients complained of a colicky abdominal pain just before defecation or, rather, the pain was always accompanied by a desire to defecate. Movement of the bowels usually brought relief, especially if accompanied by the passage of flatus. One of our patients (Case 22) complained of frequent abdominal pain, without any desire to defecate. Occasionally, the symptoms are rather those of great frequency and urgency (Case 23). Tenesmus is present usually when the rectum is involved. In one of our very interesting cases (Case 25), the pain was more marked after stool, radiating up the back and down both thighs. After passage of blood and mucus, there was always a feeling of unfinished stool. Case 34 gave a history of blood and mucous diarrhea entirely unaccompanied by pain. In most patients, the attacks of abdominal pain are short lived, but recurrence is the rule.

15 Schmidt, A. I. Klinik der Darmkrankheiten, 1921.

Abdominal Tenderness—Only one patient (Case 41) in our series gave evidence of abdominal tenderness. Postmortem examination showed the presence of a perforation of the cecum close to the base of the appendix.

Incontinence—Four cases (Cases 38, 41, 26 and 39) of the more severe type showed incontinence for long periods during their illness. The loss of sphincter control is often associated with severe debilitating chronic diarrheal conditions.

Vomiting—In two cases (Cases 39 and 12), this symptom was a troublesome one. Vomiting is not a constant feature in nonspecific ulcerative colitis, and, if present, is probably due to the absorption of toxic material from the intestine.

Loss in Weight—This is noted in practically every case, and often becomes a serious factor in the prognosis. Table 6 indicates the result of a survey of our series.

TABLE 6—*Loss of Weight in Nine Cases*

Case	Loss in Pounds (Kilograms)	Period
3	11 (5)	8 months
6	20 (9)	6 years
8	10 (4.5)	1½ years
9	19 (8.6)	1 year
15	25 (11.3)	5 months
18	35 (15.9)	1 year
20	50 (22.7)	7 years
26	35 (15.9)	1 year
33	17 (7.7)	1½ years

Two of our patients showed no loss in weight. The remainder, not included in Table 6, lost weight, but no fairly accurate estimate could be made. It should be remembered that many of these patients place themselves on a very restricted diet and this, in conjunction with loss through diarrheal stools, often leads to marked reduction in weight.

Fever—Three of our patients (Cases 20, 21 and 33) experienced chills, either at the onset of the first attack or during recurrence. Most cases show a moderate rise in temperature, the average being somewhere between 100 and 101 F. Some cases show an absolutely normal temperature curve. Sharp rises will occur, however, with complications, such as perforation or intramural abscess. Figure 2 is illustrative of rises in temperature due to the formation of intramural abscesses.

In the average patient, the affection seems to run a rather subacute course with little or no hyperpyrexia. One patient (Case 15), who subsequently became entirely well, ran a temperature of 95 F on two occasions.

Sigmoidoscopic Examination—As only one of our cases came to necropsy, the following descriptions of individual cases may be of interest.

CASE 1—The mucosa of the colon was very boggy and bled easily. The entire field was covered with purulent and bloody exudate. Above 8 cm., no bleeding was seen, but a whitish fluid was present.

CASE 3—Scattered irregularly over the rectum and a large part of the sigmoid, sometimes in groups, elevated irregular papules with whitish necrotic tops were to be seen. The mucosa also showed some irregular, small, clean ulcers. There appeared to be an unusually small amount of inflammatory reaction present.

CASE 4—The mucous membrane showed irregular ulcerations (denudation). There were also elevated granulation areas surrounded by depressions, in

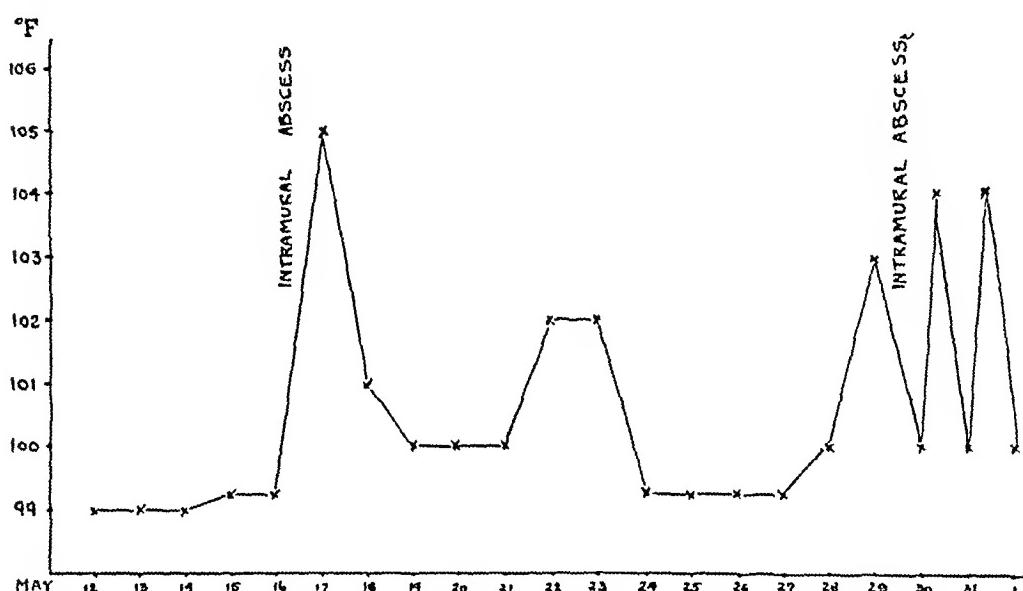


Fig. 2 (Case 16)—Temperature chart in case of intramural abscess. A similar condition occurred at the time of this patient's previous admission, when the temperature rose rather suddenly from 99 to 103 F, lasting twenty-four hours and coming down, by lysis, during a period of about a week.

which pus might be seen. The ulcers partially surrounded the bowel in several places.

CASE 5—The internal sphincter muscle was almost destroyed (previous operative procedures). On digital examination, one could detect a "lumpiness" of the bowel, with intervals of smooth mucosa as far as the fingers could reach. On the left side, parallel with the 8 or 9 o'clock position of a clock hand, was a large inflammatory mass. The bowel was covered with mucus, pus and blood, principally in the inflamed region. The inflamed area seemed to follow the course of the blood vessels on the outside. There were some linear, serpiginous inflamed areas. Here and there, one saw prominent longitudinal masses, about the size and shape of the first phalanx of the index finger, composed of pinkish granulation tissue which was almost cartilaginous to the touch.

CASE 7—The mucosa was very red and angry looking, and was covered with great quantities of mucus. There were a few scattered ulcerated areas to be seen. The entire mucosa bled very easily.

CASE 10—The mucosa was edematous and vesicular and oozed a sero-sanguineous fluid. It bled easily, and was covered irregularly by a flocculent, grayish white membrane. On the edge of the valve was seen a definite shallow ulcer. Grayish white spots floated on top of the serous exudate, giving the mucosa a speckled appearance.

CASE 16—Many small ulcers were present, extending from the sigmoid to the anal margin. Some of these ulcers were covered with whitish membrane, but the majority were filled with granulation tissue. When membrane is present, it is stained with blood and, on removal, leaves a raw, denuded surface.

CASE 18—Segmental infection was present, beginning at a point 9 cm from the anus and extending up to 30 cm. The rectal area showed evidence of previous infection. There were denuded ulcerated areas extending from a point about 12 cm from the anus to the apex of the sigmoid, and probably much higher. In the rectum, these ulcers circumvented the wall. A large amount of reddish, thick fluid was present (blood and detritus). At about 10 cm, there was a partial stenosis through which exuded an admixture of pus and blood.

CASE 21—The mucosa of the colon was extremely red, of granular appearance, and covered with pus, mucus and blood. This condition existed as far as one could reach with the sigmoidoscope, and probably extended as far as the cecum.

CASE 24—The rectal and sigmoidal mucosa appeared to be acutely inflamed. An occasional ulcer might be seen. At a point just above the internal sphincter on the left side, there was an ulcerated area 4 cm in length. The entire inflamed region was covered with pus and blood. All the ulcers were necrotic and irregular.

CASE 31—In this case, almost all the lesions were confined to the rectum. Here, the mucosa appeared red, boggy and edematous. The slightest pressure caused pain. Numerous long, sharply defined ulcers were present. In some places, the mucosa was covered by a whitish membrane which resembled macerated skin. Most of the ulcers were on the anterior surface of the rectum, which was covered by a large quantity of pus and blood.

CASE 33—The colon was covered by a thick exudate. Epithelial cell masses floating on the top of this fluid gave the bowel a bosselated appearance. On removing the exudate, the wall presented a granular appearance. The mucosa bled easily.

CASE 36—The mucosa was very edematous. Clusters of papules were irregularly distributed from the anus to the sigmoid. These could be seen in their various phases, beginning with papules and going on to vesicles, papules with necrotic tops and papules with regular craters having a smooth round wall, sloping symmetrically toward the center. In places, the lesions had reached the ulcerative stage, especially on the edge of the first valve. Here, the ulcerative process was irregular and had a tendency to extend circumferentially rather than longitudinally. The whole area was covered by mucus, pus and serum.

CASE 38—Ulcers were seen scattered here and there, interspersed with polyps, varying in size from 1 to 20 mm. There was also seen one granular, confluent ulcer covered with exudate, which consisted of blood, mucus and pus. At a point 7 cm from the anus, there was a stricture 6 cm in length.

The foregoing cases have been chosen as illustrating the variety of lesions one may expect to see in the course of sigmoidoscopic examination.

Blood Changes—Most cases present a secondary anemia of moderate severity. Cases have been reported, however, in which the anemia has

been so severe as to resemble pernicious anemia. Three of our patients (Cases 20, 30 and 34) showed a marked anemia and two of these (Cases 20 and 30) subsequently died of pneumonia. The figures for these two fatal cases were as follows: Case 20 hemoglobin 38 per cent and erythrocytes, 2,300,000 per cubic millimeter. Case 30 hemoglobin 35 per cent, and erythrocytes, 2,160,000 per cubic millimeter.

Miscellaneous Laboratory Data.—In only one case (Case 31) was there any history or laboratory evidence of syphilitic infection. Dec. 7, 1912, the blood and spinal fluid gave a positive Wassermann reaction. The spinal fluid showed a cytology of 181 cells per cubic millimeter, and globulin was present. April 14, 1914, after intensive aiphenamin therapy, the blood and spinal fluid examinations proved entirely negative. Spinal fluid cytology was 4 cells per cubic millimeter and globulin was



Fig. 3.—Sigmoidoscopic picture in idiopathic ulcerative colitis absence of granular appearance of mucosa

absent. The onset of illness occurred one year later and all examinations seemed to point to the nonspecific nature of the colon infection.

Most of our cases showed some albumin and occasional casts in the urine at some time during the period of observation. Blood chemical studies, gastric analysis and basal metabolism determinations proved to be negative.

Roentgen-ray examinations may show absence of normal haustration, motting of the wall due to ulceration and abnormal narrowing of the intestine due to spasm.

DURATION AND COURSE OF NONSPECIFIC ULCERATIVE COLITIS

If one disregards the duration of acute attacks and bases his estimate entirely on sigmoidoscopic or operative findings he will be impressed by the great variations in the duration and course of this infection. Much depends on the type of treatment instituted. Patients left to heal spon-

taneously without medical or surgical intervention almost invariably fare badly. Others on whom the proper treatment has been instituted may clear up in a few weeks or go on for years with periodic acute exacerbations. Some do not get along no matter what procedure is followed, and this applies especially to cases which have come under observation late in the disease, when the infection has already spread to the small intestine. Undoubtedly, the factor of individual resistance to disease plays a great part in the healing process in ulcerative colitis. The poorly nourished, weakly, sallow patient almost always has a hard struggle to overcome this condition. Recurrence and chronicity are typical of nonspecific ulcerative colitis. Yeomans¹³ reports an average duration of two months. In our series, the average period of duration was ten months if reckoned from the date the patients first came under our observation and treatment until complete healing occurred, as evidenced by the sigmoidoscopic examination and disappearance of symptoms.

TABLE 7.—Duration of Disease from Time Treatment Was Instituted Until Apparent Cure

Case	Duration	Permanence to Date
1	1 month	1½ years
2	3 months	7½ years
3*	2 months	1½ years
7	1 month	1 month
9	2 years	4½ years
11	4 months	3½ years
21	2 years	5 years
31*	2 months	5 years
35	2½ years	8 years
40	1 year	1 year

* Subsequent recurrence with recovery.

Sixteen patients were discharged improved, but not entirely healed. Nearly all of these, for some reason or other, could not remain in the hospital long enough to complete treatment. Nine patients left the hospital unrelieved after a short stay (incomplete treatment), and have not been accounted for since discharge. Five patients remained unrelieved and subsequently died.

The clinical course of the disease, aside from the features above described, depends almost entirely on the local pathologic condition. If the lesions are progressive, intramural abscesses of the colon may form (Fig. 2). Further extension will involve the peritoneum or neighboring viscera.

PROGNOSIS

From our experience with this condition, we are inclined to make a rather guarded prognosis as to permanence of cure. The brilliant results obtained by colonic irrigations tend to make one overenthusiastic. The ten cases showing complete healing have remained apparently

entirely well for periods varying from one to eight years (except a recent one, Case 7, which has been followed up for only one month) As shown in necropsy reports, there is a tendency for the ulcerative lesions to heal spontaneously so that there is a possibility that in mild cases, the patients never seek medical attention In any case, one should advise the patient of the long, painstaking course of treatment, though one may be occasionally agreeably surprised at the rapidity of healing in even the most chronic cases

CAUSES OF DEATH

The causes of death in our cases were as follows in Case 8, volvulus of the small intestine, Case 20, pneumonia, Case 22, extension of infection to the small intestine, Case 27, postoperative (ileostomy) dilatation of the stomach, Case 41, perforation of the cecum, and Case 30, pneumonia



Fig 4.—Sigmoidoscopic picture in idiopathic ulcerative colitis, granular appearance of mucosa

OPERATIVE FINDINGS

CASE 3—Ileostomy was done The sigmoid and lower 6 inches (15.2 cm) of the ileum was much thickened

CASE 27—Ileostomy was done The colon was enormously thickened Fifteen inches (37.5 cm) of the small intestine was involved

CASE 21—Removal of cecum was done The mucosa was acutely inflamed and hemorrhagic The entire wall of the cecum was edematous

BACTERIOLOGY OF NONSPECIFIC ULCERATIVE COLITIS

A review of the bacteriology of nonspecific ulcerative colitis is a study of the bacteriology of the colon Our knowledge as regards the latter is very limited,¹⁵ as there are any number of organisms in the feces which have not yet been identified or definitely classified This is especially true of the gram-positive bacillus group It has been observed

by Kendall¹⁶ and others that changes in the intestinal flora depend somewhat on the diet of the person. It is interesting to note the heterogeneous variety of intestinal bacteria in the adult on the usual mixed diet as compared with the homogeneity of types found in the nursing infant. Under normal conditions in the adult, *Bacillus coli* comprises about 75 per cent of the viable bacteria of the feces. The cecum and the ascending colon are the regions of most intense bacterial growth in health, but the number of living bacteria diminish abruptly from the sigmoid to the rectum, where the feces are fairly well desiccated.

The stomach, in health, is practically free from bacteria. Studies by Kendall have shown that the most common bacteria in the duodenum are the enterococcus and members of the *mucosus capsulatus* group. As we advance down the small intestine the cocci still predominate as far as the upper ileum, but a moderate number of organisms of the colon group begin to appear. In the ileocecal region, the flora is usually represented by the aerogenic bacilli of the colon type and spore bearers of the mesenteric group. In the colon, we obtain facultative-fermentative bacteria—the colon-proteus group, various aerobic liquefying bacilli (both spore bearing and nonspore bearing) and some anaerobic bacteria. The change in bacterial flora, as we advance down the intestinal tract, may be of prime importance in explaining the limitation of the lesions to the colon. This phenomenon may also account for the comparative immunity of the normal adult to intestinal infection. To quote Kendall¹⁶:

It is probable that the significance of the intestinal flora lies rather in its potential antagonism to alien bacteria, which certainly gain entrance to the alimentary canal from time to time, than in any specific participation in the normal digestive process of the host. The normal intestinal flora may be regarded as intestinal parasites, just as the various bacteria which occur commonly on the skin are regarded as cutaneous parasites. It is important to realize that the normal intestinal organisms, like the cutaneous organisms, are opportunists, potentially capable of becoming invasive whenever the barriers which ordinarily suffice to limit their development to the lumen of the alimentary canal become impaired, giving rise to endogenous infection.

It was shown by Levin, who investigated the bacteriology of intestinal contents of Arctic animals at Spitzbergen, that, in most instances, the digestive tracts were entirely sterile. Thus, it seems quite certain that intestinal bacteria are not essential to life. If we assume (and our assumption may be incorrect) that the normal dominating organism in the colon (*Bacillus coli*) plays the part of a protector against dangerous foreign invaders, then it is logical to suppose that we must look elsewhere than for *Bacillus coli* as the etiologic pathogenic agent in ulcer-

tive colitis. Thus, Herter quotes a case of colitis in which *Bacillus coli* had been replaced by another organism as the dominant type. Recovery ensued when *Bacillus coli* had been again restored. Unfortunately, in our studies, we have failed to discover any displacement of *Bacillus coli* from its normal role. In general, most bacteriologic studies in non-specific ulcerative colitis have been very unsatisfactory. Table 8 gives the results of bacteriologic investigation in eleven of our cases.

PATHOLOGY OF NONSPECIFIC ULCERATIVE COLITIS

Gross Pathology.—The pathologic process probably starts as an acute inflammation of the mucosa of the colon. This is followed by small patches of localized necrosis and sloughing off of the dead mucosa,



Fig. 5.—Sigmoidoscopic picture in idiopathic ulcerative colitis, showing tendency of such ulcers to become confluent. Such ulcers may even circumscribe the intestinal wall, leaving only small islands of intact mucosa; pus, mucus or blood may cover the surface.

leaving an ulcerated area which usually has the submucosa as a base. Recent ulcers are fairly clean cut, the edges are not undermined and vary in size, from a few millimeters to extending transversely around the colon. The tendency is to remain superficial and often adjacent ulcers coalesce, forming irregular, mapped out areas, with portions of intact mucosa between them. Often the intact mucosa appears to be undermined by the spreading ulcers, and, becoming edematous gives the appearance of polyp formation. Hewitt and Howard¹⁷ believe that, as healing begins, the margins of intact portions of mucosa are smoothed off, and the polypoid projections result. Often at a later period orifices of secreting tubules in the mucosa become blocked off by contraction of

¹⁷ Hewitt, J. H., and Howard, W. T.: Chronic Ulcerative Colitis with Polyps, a Consideration of the So-Called Colitis Polyposa (Virchow), Arch. Int. Med. 15: 714 (May) 1915.

scar tissue resulting in small retention cysts. This corresponds to the "colitis polyposa cystica" of Virchow. In the process of healing, new mucosa forms, and very little scarring results. Sigmoidoscopic examination may reveal only a few puckered areas or pigmented spots in the mucosa. In the more severe cases, the muscularis may form the floor of the ulcer and the peritoneum over this area may be reddened. Perforation may occur with local or generalized peritonitis. Multiple perforations are rare. In one of our cases, the cecum was involved, and the subsequent infection and necrosis resulted in a sudden extrusion of fecal material into the abdominal cavity. Some authors have described cases in which the colon wall was softened to such a degree that the palpating finger tore through it. It should be remembered that, in the

TABLE 8.—*Bacteriologic Studies in Nonspecific Ulcerative Colitis*

Case 3—Feces Gram-positive bacilli, 5 per cent, gram-negative bacilli, 55 per cent, gram positive cocci 40 per cent
Case 7—Purulent material from ulcerated area on colon. Heavy growth of coliform bacilli practically crowding out the usual gram positive bacteria. No streptococci or staphylococci found. No <i>Bacillus dysenteriae</i> present
Case 10—Feces <i>Bacillus coli communis</i> obtained in pure culture
Case 15—Feces <i>Bacillus coli communis</i> predominate in culture
Case 16—Feces <i>Bacillus coli communis</i> predominate. There are also two or three gram positive organisms present, one of them a spore bearer
Case 21—Pus from cecum removed at operation. <i>Bacillus coli communis</i> predominate. Undifferentiated short, slender bacillus and a large diplococcus are also present
Case 25—Feces Gram negative bacteria, 15 per cent, gram-positive bacteria 85 per cent
Case 42—Pus from rectum. Diphtheroid organisms associated with <i>Bacillus coli communis</i> . No phagocyted bacteria are seen, which suggests that the significant organism may be <i>Bacillus coli communis</i>
Case 30—Feces Gram negative micrococci, unidentified (this patient was a baby 21 months old)
Case 32—Feces <i>Bacillus coli-communis</i> and staphylococci predominate
Case 37—Intestinal exudate <i>Bacillus proteus</i> , <i>Bacillus mucosus capsulatus</i> , <i>Bacillus coli communis</i> and <i>Streptococcus viridans</i> predominate

average case, one may see ulcers in all stages of development—some small, round or oval, superficial ulcers, others irregular or deep and spreading, and still others in various stages of healing. In all cases, the mucosa is intensely congested. The mesenteric glands are rarely involved. The small intestine is rarely affected. Liver abscess is an unusual complication. Except possibly for a fatty liver, the remaining organs are in a surprisingly good state in the average case.

It might be well to mention, at this point, a condition often described as follicular colitis. Here the solitary follicles situated in the mucosa of the colon and rectum are the seat of lesion. The swollen follicles cause a pressure necrosis in the overlying mucosa giving rise to small, rounded, well defined ulcers, usually located along the line of the mesentery or of the longitudinal folds. This condition is fairly frequent in fatal nonspecific diarrheas of children.

Histopathology—Sections of colon taken from ulcers and surrounding areas, show, first, an acute inflammation of the mucosa which becomes red, swollen and may be the seat of small hemorrhages. Numerous leukocytes are to be seen. The submucosa and muscularis are infiltrated with leukocytes and plasma cells. There is dilatation of the blood and lymph vessels. Soon the mucosa becomes necrosed and is cast off, leaving a very superficial ulcer. The epithelium of Lieberkuhn's crypts may be only the seat of cloudy swelling, or else may be destroyed in the ulcerative process. The mucosa in other areas may be atrophic. Granulation and foreign body giant cells may be present in ulcerated regions.

In follicular colitis, the pathologic process is similar, except that it starts in the solitary follicles, which become hyperplastic and infiltrated with small round cells. The overlying mucosa becomes necrotic, and



Fig 6.—Sigmoidoscopic picture in follicular ulcerative colitis, punched out appearance of ulcers, which correspond in position to solitary follicles

the follicle ruptures, resulting in a discrete, superficial, round ulcer with a flat base.

THEORIES AS TO THE ETIOLOGY OF NONSPECIFIC ULCERATIVE COLITIS

Theories concerning the cause of this obscure condition are still rather vague, but we have often thought of several possibilities.

Constitutional—The frequency with which this disease attacks run down, debilitated and insane persons suggests the possibility of some underlying constitutional factor. There may be absent from the wall of the colon, under abnormal conditions, certain substances which normally protect the mucosa against injury by harmful food substances or possibly digestive juices within the colon. Some have considered the condition in the insane as being essentially a trophic disturbance.

Traumatic—The frequency with which intestinal mucosa is exposed to mechanical injury suggests this theory. There may be only a minute denudation of mucosa which could be caused by the edge of an apple seed or other débris. Yet this might be sufficient to give virulent pathologic organisms within the intestine an opportunity to obtain a foothold, and give rise to inflammation of the mucosa, or the bacteria may play a minor part and the digestive juices or proteolytic ferments give rise to an ulcerative process.

Excretory—It is possible that toxic substances, metabolic or bacterial, excreted through the wall of the colon can result in ulcerative lesions. Flexner and Sweet¹⁸ have shown this to be true for the toxin of *Bacillus dysenteriae*.

Bacterial—As suggested in the discussion on the bacteriology of nonspecific ulcerative colitis, under abnormal conditions, pathogenic bacteria, which ordinarily lie dormant, may suddenly predominate in the intestinal flora and exert a direct harmful action on the wall of the intestine. Occasionally, one receives the impression that even *Bacillus coli*, under certain conditions, may become pathogenic. A point in favor of this theory is the report of success in some cases by the use of *Bacillus coli* vaccine.

TREATMENT

Medicinal—These measures are directed chiefly toward influencing the bacteriology of the affected region and to relieve discomfort.

(a) Colon Irrigation—Colon irrigations have proved very effectual in our cases and bring about rapid relief or possible cure. Various substances have been used (silver nitrate, silver nucleinate, boric acid, physiologic sodium chloride solution, sodium bicarbonate, quinin and water), but we have found potassium permanganate, peroxid of hydrogen and chloramin-T best. Of the latter three, potassium permanganate irrigation is our method of choice. The colon should be as empty as possible before injection. The patient is placed in the knee-elbow position, with thighs perpendicular to the bed, back concave and shoulders resting on the bed (in order to reduce the natural obstruction at the sigmoidorectal flexure). The tip of the nozzle is introduced about 1½ to 2 inches (3.7 to 5 cm.) inside the rectum, and large quantities of potassium permanganate solution are injected—several quarts if possible. We start with 1 10,000 solution, and gradually work up to 1 5,000. The irrigations are given three times a day, and retained each time for an hour (this is more easily accomplished if the tube is left in position).

¹⁸ Flexner, S., and Sweet, J. E. The Pathogenesis of Experimental Colitis, and the Relation of Colitis in Animals and Man, *J. Exper. Med.* 8: 514-535, 1906.

It is often surprising what a good result one may obtain by suddenly switching from permanganate to peroxid or chloramin-T. It is possible that these strong oxidizing agents affect the bacteria directly, especially the anaerobes.

(b) Diet The idea is to endeavor to furnish a diet which will favor the development of normal intestinal bacteria. Thus, if the flora is essentially putrefactive, the protein should be largely eliminated from the diet. So, too, in the fermentative diarrheas, the carbohydrates should be curtailed.

(c) Ingestion of Harmless Bacteria to Replace Harmful Flora Herter¹⁹ was the first to recognize the possibility of introducing desirable types of bacteria into the intestine. This method has practically

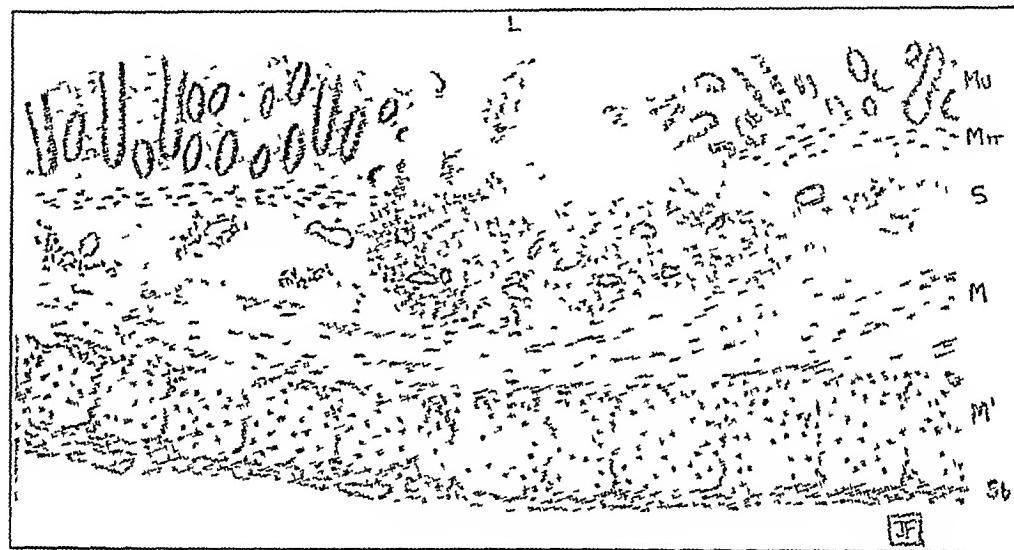


Fig 7.—Histopathologic picture of typical ulcerated area in case of idiopathic ulcerative colitis. L, ulcerated area; Mu, mucosa; Mm, muscularis mucosae; S, submucosa; M and M', muscularis, and Sb, subperitoneal connective tissue. In the process of healing, the necrotic tissue is removed, the area granulates and epithelializes over until, in most cases, restoration of normal contour is complete.

narrowed itself down to *Bacillus acidophilus*. This may be taken in whey or broth cultures, or in the form of acidophilus milk. The proteins in the diet should be cut down and large amounts of lactose administered to help assure permanence of these bacilli in the colon.

(d) Vaccine Numerous observers have reported good results with *Bacillus coli* vaccine, preferably made up of many strains. Our experience has been very limited.

Serums and antitoxins should be theoretically useful, but, except in the case of bacillary dysentery, they have not yet been successfully

¹⁹ Herter, C A. On Certain Relations Between Bacterial Activity in the Intestine and the Indican of the Urine, Brit M J 2 1847-1849, 1897.

prepared Morphin or other opium preparations have been used to relieve acute symptoms

Surgical—Various procedures have been used with more or less success These are early appendicostomy or ileostomy, complete transverse colostomy and, in cases in which the entire colon is involved, colectomy

Complete diversion of the intestinal contents or entire removal of the affected area seem to be the most logical procedures, but, unfortunately, these are usually accompanied by a rather high mortality In cases not yielding to medicinal therapy, ileostomy is our method of choice At a later period, colectomy is to be preferred

CONCLUSIONS

1 A clinical and pathologic review of forty-one cases of non-specific ulcerative colitis shows this affection to be a distinct clinical entity of obscure origin

2 In our hands, the best results have been obtained by means of colonic irrigations

Future studies will be mostly devoted to more detailed laboratory investigations, with a view to ascertaining a possible specific etiologic agent

THE ELECTIVE LOCALIZATION OF BACTERIA IN PEPTIC ULCER *

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One of the numerous theories of peptic ulcer is that bacteria are an important etiologic factor. Just how great a part bacteria play is, however, a debated and undetermined question. Bevan¹ thinks that hematogenous septic infarcts of the mucosa may have a rôle but are not the common cause. Eusterman,² on the other hand, states that "the theory that infection is the cause of ulcer is admittedly the only tenable one at this stage of medical progress." Between those two diverse views is the classification of Smithies,³ who divides ulcer from the standpoint of etiology into ten groups, and classifies one third of the total number as bacterial in origin.

Experimental data concerning the infectious theory of ulcer are due almost entirely to the work of Rosenow, who has shown that the intravenous injection of streptococci may be followed by ulcer of the stomach and duodenum, that streptococci are commonly found in the ulcer of man, and that the injection of streptococci isolated from the ulcer wall as well as from foci of infection in patients suffering from peptic ulcer produces, when injected into animals, ulcers of the stomach and duodenum resembling those of man.⁴

The best proof of a causal relationship of bacteria to systemic disease is the reproduction of the patient's lesion in animals by the injection of bacteria isolated from septic foci in the patient. Ability to so reproduce lesions is of interest not only as proof of an etiologic relation of the bacteria to the disease but also as evidence of a specific tendency of different strains of bacteria to cause certain diseases. Such a specific tendency is the elective localization of bacteria in the sense of Rosenow.

Rosenow, in a mass of experimental work, has produced convincing evidence to support the idea of elective localization. The theory has not found acceptance, however, at the hands of many other research workers largely because few have been able to verify Rosenow's experimental results. I have discussed elsewhere the literature concerning this point.

* From the Deane Institute

1 Bevan, A D Relative Value of Surgical and Medical Treatment of Gastric and Duodenal Ulcer, J A M A **79** 22 (July 1) 1922

2 Eusterman, G B Minnesota Med **6** 698 (Dec) 1923

3 Smithies, Frank Significance of Etiologic Factors in Treatment of Peptic Ulcer, J A M A **74** 1555 (June 5) 1920

4 Rosenow, E C J Infect Dis **19** 333 (Sept) 1916, ibid **19** 527 (Oct) 1916 Rosenow, E C Surg, Gynec & Obst **33** 19 (July) 1921 Rosenow, E C J Infect Dis **33** 248 (Sept) 1923

and reported a series of eye infections,⁵ several cases of pyelonephritis⁶ and two cases of multiple onychia⁷ studied from the standpoint of elective localization. In these experiments, there was an unmistakable tendency of the bacteria to reproduce, on intravenous injection, the type of lesion from which the patient suffered. I have pointed out what is perhaps the fundamental obstacle to the reproduction of specific lesions in animals, namely, the failure of most workers to use culture mediums furnishing graded oxygen tension. This point has also been emphasized by Rosenow.

Recently, I have been studying a series of patients suffering from peptic ulcer to determine whether bacteria isolated from areas of dental infection in such patients would tend to produce gastroduodenal lesions in animals. The results are of interest from the standpoint of the theory of elective localization of bacteria and of the infectious origin of peptic ulcer.

Rosenow has reported, in several papers, his studies of elective localization in peptic ulcer. He found that 68 per cent of 168 animals injected with thirty-seven strains of streptococci from patients with gastric ulcer had lesions of the stomach, while only 15 per cent of a series of control animals injected with bacteria from patients with myositis had gastric lesions.⁸ Nakamura,⁹ working in Rosenow's laboratory, injected sixty-six animals with cultures from the tonsils in cases of gastric ulcer and found gastroduodenal lesions in 70 per cent. Similar lesions were found in 25 per cent of control animals injected with tonsil cultures from other patients. Rosenow has made the observation¹⁰ that the specific tendency to localize in the gastric mucosa may last as long as eight and one-half years, when the infecting bacteria are kept under anaerobic conditions. He also has found that the streptococci of ulcer produce free, in broth cultures and likewise in their substance a poison that selectively injures the mucosa, since lesions can be produced by broth filtrates and by dead cultures.

METHODS

In the work here reported, I have followed closely certain fundamental technical details insisted on by Rosenow and usually disregarded by those attempting to repeat his work. All cultures have been made in glucose brain broth and glucose brain agar, mediums which provide every

5 Haden, R. L. Elective Localization in Eye of Bacteria from Infected Teeth, *Arch. Int. Med.* **32**: 828 (Dec.) 1923.

6 Haden, R. L. *Am. J. M. Sc.*, to be published.

7 Haden, R. L., and Jordan, W. H. *Arch. Dermat. & Syph.* **8**: 31 (July) 1923.

8 Rosenow (Footnote 4, second reference).

9 Nakamura, T. *Ann. Surg.* **76**: 29 (Jan.) 1924.

10 Rosenow (Footnote 4, third reference).

degree of oxygen tension. The exact method of preparation has been described elsewhere.⁵ The original broth cultures have been injected into animals as soon as good growth was obtained. This was usually from fifteen to twenty-four hours after the culture material reached the laboratory.

Before extraction, the tooth to be cultured was scrubbed with gauze and painted well with tincture of iodin followed by alcohol. The area of operation was walled off with sterile gauze. After removal, the tip of the tooth was cut off with sterile forceps directly into a test tube containing a few cubic centimeters of sterile physiologic salt solution and a small amount of sterile sand. The tubes were then well shaken to macerate the tissue on the tip of the tooth as completely as possible. The mediums are inoculated by pouring the salt solution containing the suspended tissue into a deep tube of glucose brain agar previously heated and cooled to 40 C. The tube is quickly inverted twice and allowed to harden. The small amount of salt solution remaining in the tube is poured into a deep tube of glucose brain broth. The inoculated tubes are incubated from twenty-four to forty-eight hours. A smear is made from the broth culture and stained by Gram's method. A transplant of the broth culture is made to a blood agar plate. The appearance of a culture in a deep tube of glucose brain agar is shown in Figure 1, B. This culture is from the left lateral incisor shown in Figure 1, A. It is from one of the patients reported in this series (Case 1), and is of special interest in that the organism will not grow in the strictly aerobic portion of the tube. This organism would grow poorly, if at all, on open plates. Even if a culture on open plates were successful, it is very probable that the tendency to produce specific lesions would have been lost.

Rabbits have been injected intravenously with the original broth culture. When cultures were taken from several teeth from one patient the several broth cultures often were mixed before injection. The animals varied somewhat in size but averaged about 1,500 gm. Each animal was given 5 cc of the broth suspension.

The animals were killed from two to four days after injection, and carefully examined for lesions in all organs. No lesions were considered as present unless plainly visible to the naked eye of at least two observers. Microscopic sections were made from some of the tissues but not as a matter of routine.

EXPERIMENTAL OBSERVATIONS

Twelve patients have been studied. Streptococci were grown from the root tip of one or more teeth or from areas of infected bone in each case. In some cultures staphylococci were recovered with the streptococci. The streptococci were usually of the nonhemolytic type. In only

one instance (Case 2) were hemolytic organisms found. Some of the nonhemolytic streptococci were of the green producing type, others were indifferent on blood agar.

Forty-five rabbits were injected intravenously with the broth cultures. At least two rabbits were injected from each patient. Twenty-four, or 53 per cent, of the animals showed at necropsy lesions in the stomach or duodenum or both, as shown in the accompanying table. There were positive findings in at least one animal from each patient. During the period covered by these experiments, 535 other rabbits were injected similarly with cultures from the dental foci of 191 patients not known to be suffering from peptic ulcer. Of these, forty, or 7 per cent, showed at necropsy lesions in the stomach and duodenum. This figure (7 per cent) can be taken as the normal incidence of peptic lesions on routine intravenous injection apart from any specific tendency to localize.

Localization of Bacteria from Dental Infection on Intravenous Injection in Rabbits

Group	Number Animals Injected	Number Patients	Percentage of Animals Showing Lesions in							
			Joint	Muscle	Kidney	Endo cardium	Myo cardium	Stomach and Duo denum	Brain	Eye
1*	535	191	57	27	38	18	11	7	7	23
2†	45	12	36	27	22	9	18	53	4	11

* Group 1, animals inoculated with dental cultures from patients not known to be suffering from peptic ulcer.

† Group 2 animals inoculated with cultures from teeth of patients suffering from peptic ulcer.

The table details also the percentage of animals having lesions in other organs. The animals in Group 2 show a lower percentage of lesions in other organs, except the muscle, which is the same, and the myocardium, which is higher. In numerous instances in Group 2, the rabbits had no lesions other than those of the stomach and duodenum. The fact that many animals show other lesions also is no argument against the theory of specific localization. Many of the patients likewise presented symptoms of other systemic disease of focal origin coincident with the peptic ulcer.

The anatomic lesions, as observed grossly, were usually hemorrhagic with or without ulceration. The lesions in the stomach nearly always showed ulceration or at least erosion. The hemorrhage in the duodenum usually was not followed by gross ulcer formation. The course of the pathologic process after the initial injury depends largely perhaps on the amount of free hydrochloric acid present. In some animals, the lesions consisted principally of necrosis in the muscle wall, a type of lesion commonly found in the voluntary muscle of the rabbit after intravenous injection.

Sections of the involved parts show hemorrhage, polymorphonuclear infiltration and necrosis of the mucosa (Fig 6). The pathologic process is usually quite diffuse and evidently not usually dependent on thrombosis or embolism. It is often assumed that damage here by bacteria must result from one or the other of these two conditions. A study of the sections does not bear out this assumption. This is especially true of duodenal lesions. Judd¹¹ has pointed out that very commonly patients diagnosed clinically as having duodenal ulcer are found, at operation, to have a diffuse duodenitis without ulceration. The lesion observed in the duodenum of animals is usually a duodenitis of such a type.

COMMENT

In this series, 53 per cent of the animals showed lesions of the stomach and duodenum after the intravenous injection of bacteria recovered from chronic foci of infection in dental areas of patients suffering from peptic ulcer. Only 7 per cent of animals similarly injected with cultures from patients not known to be suffering from peptic ulcer developed lesions of the stomach or duodenum. Such evidence is very strong proof of Rosenow's idea that the bacteria concerned in peptic ulcer show a specific tendency to localize in the gastroduodenal region. The findings thus support the theory of the elective localization of bacteria.

The experimental data reported here is also good evidence in favor of the infectious origin of peptic ulcer. The frequent manifest improvement in the patient's condition following the removal of chronic infection is the final link in the chain of evidence. Such improvement was apparent in many cases of this series.

Another point in favor of the causal relation of chronic focal infection to peptic ulcer and also of the theory of elective localization is the anatomic location of the gastric and duodenal lesions in the experimental animals. It is well recognized that gastric ulcer may occur in any part of the stomach but is much more frequent in the pyloric region. The experimental gastric lesions have a similar distribution. Clinically, duodenal ulcer is always limited to the first third of the duodenum. The usual explanation given for this localization is that only in this portion is free hydrochloric acid present, and that here the gastric contents are retained longer than in any other portion of the duodenum. In every animal but one in which duodenal lesions were observed, the involvement was limited to the duodenal bulb. The one exception was a very extensive lesion extending from the pyloric ring through the greater part of the duodenum (Fig 4, B).

Several points in regard to the relation of dental infection to peptic ulcer should be emphasized. Not infrequently, infection in the maxilla or mandible at the site of extraction of teeth harbors organisms that are the cause of systemic disease. This is well illustrated in Cases 3, 5 and 10, in this series. Often the areas from which teeth are missing are not even roentgenographed.

Usually, the roentgenologist attempts to translate changes around the teeth, as revealed by the roentgen-ray examination, into terms of numbers of bacteria. Dental infection is often ruled out because there is not roentgenographic evidence of such infection. In cultures, by a quantitative method, of the root tip of over a thousand pulpless teeth, we have been able to demonstrate that the roentgenographic negative tooth harbors infection almost as frequently as the roentgenographic positive tooth.¹² It is apparent that a pulpless tooth should not be ruled out as a possible focus of infection on roentgenographic evidence alone.

A very important factor in focal infection is the frequent multiplicity of foci. Even when such a specific lesion as gastric ulcer is reproduced in animals by the intravenous injection of bacteria from a certain focus, it is quite possible that other foci might be present and equally active. Cases illustrating this point have been reported elsewhere.¹³

SUMMARY AND CONCLUSIONS

In a study of twelve cases of peptic ulcer from the standpoint of a possible causal relation of dental infection, cultures from foci of infection in dental areas were made in glucose brain broth and glucose brain agar to provide the optimal oxygen tension. The organisms recovered were streptococci in pure culture or associated with staphylococci.

Fifty-three per cent of forty-five rabbits injected intravenously with the broth cultures from the twelve patients showed, at necropsy, gross lesions of the stomach or duodenum.

Seven per cent of 535 rabbits injected intravenously with cultures from dental infection of 191 patients not known to be suffering from peptic ulcer showed similar lesions.

The experimental duodenal lesions are practically always confined to the duodenal bulb.

The results here reported furnish confirmatory proof of Rosenow's theory of elective localization and the infectious theory of peptic ulcer.

Dental infection is an important factor in the causation of gastric and duodenal ulcer.

12 Haden, R. L. Radiology, to be published.

13 Haden, R. L. M. Clin. N. A. 7:1109 (Jan.) 1924.

REPORT OF CASES

CASE 1—J. J. W., aged 32, a plumber, gave a typical history of recurring attacks of duodenal ulcer over a period of six years. The present attack had begun five weeks before he was first seen and had been unusually severe. He was in a good state of nutrition. The tonsils were small, and no pus could be expressed. The heart sounds were clear, the pulse was 80-100, the systolic

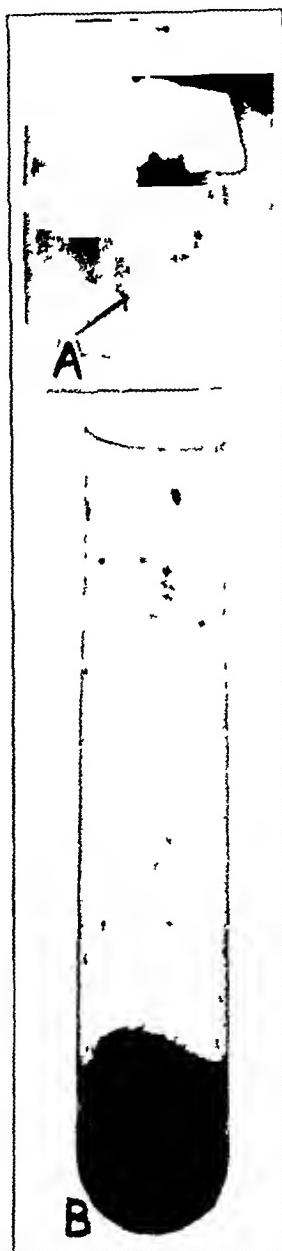


Fig. 1.—A, lateral incisors, Case 1, B, culture tube of left lateral incisor, indicated by arrow in A

blood pressure 140, the diastolic 100, the lungs were negative. There was tenderness in the epigastrium.

The roentgenograms of the teeth showed large areas of bone absorption around the lower right and left lateral incisors (Fig. 1, A). Cultures showed a profuse growth of streptococci which would not grow to the top of the culture tube (Fig. 1, B). There was also an area of questionable infection at the site of extraction of another tooth.

Animal Inoculations—Two rabbits were infected with the mixed cultures from the two incisor teeth. Both were killed the following day. One showed a massive hemorrhage in the duodenal bulb (Fig 2, A) with no lesions elsewhere. The other showed one moderate sized hemorrhage in the first third of the duodenum and a slight purulent arthritis, with no other lesions. One rabbit injected with the broth culture from the bone showed only slight involvement of the joints.

CASE 2—W. T. G., aged 43, business man, complained of a dull, burning sensation in the epigastrium, in October, 1922. The trouble came on one-half to two hours after meals and was relieved by food or soda. He had frequent heartburn but no acute pain or vomiting. The physical examination was negative, except for tenderness at the tip of the ninth rib in front, and several

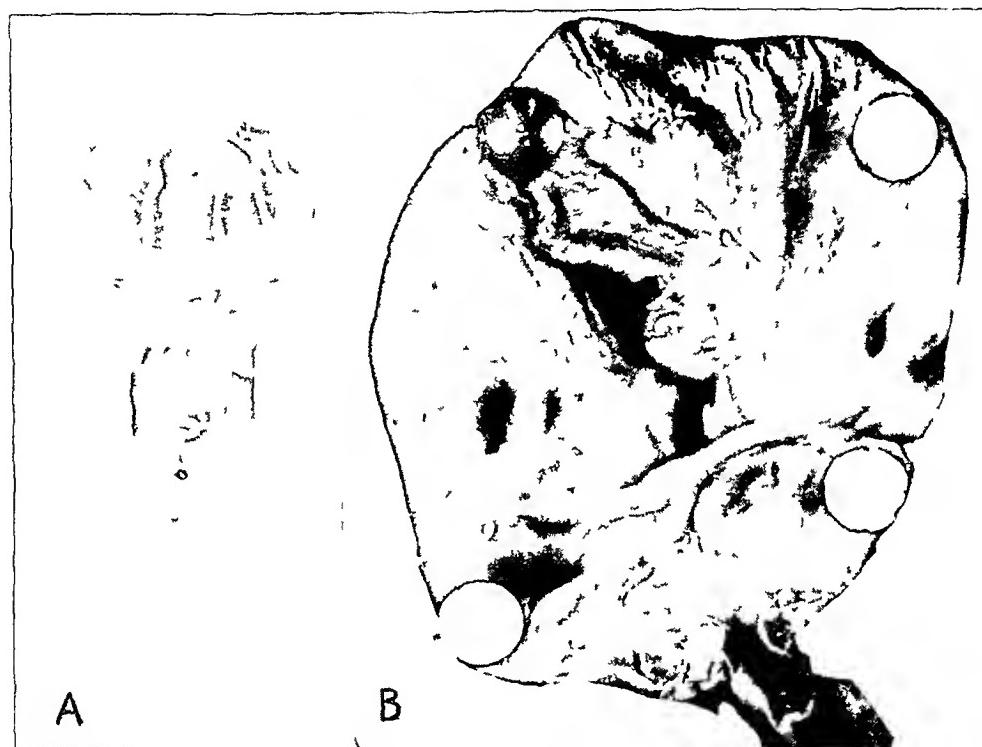


Fig 2.—A, duodenum of rabbit, following the injection of streptococcus recovered from the two lateral incisors shown in Figure 1, B, stomach of rabbit following intravenous injection of culture from cuspid shown in Figure 3, B.

pulpless teeth. The tonsils had been removed. The patient became symptom free on a special diet, until April, 1923, when he presented typical symptoms of a duodenal ulcer. Gastric analysis showed free hydrochloric acid, 40 per cent acidity, and total acid, 65 per cent acidity. The roentgenographic examination showed marked deformity of the duodenal bulb. The symptoms again disappeared under treatment. Roentgenograms of the teeth, at this time, showed three pulpless teeth with root canals completely filled. All had some bone absorption around the root tip. The three teeth were extracted. Cultures of all in deep tubes of glucose brain broth showed many colonies of bacteria.

Animal Inoculations—Two rabbits were injected with the broth culture from each tooth. Two animals showed no lesions anywhere and two, purulent fluid in the larger joints. The two rabbits injected with the culture from the upper right lateral incisor (Fig 3, B) died the day following injection. There were

many hemorrhagic areas with erosion in the stomach, some of which had progressed to ulceration (Fig 2, B) Three other animals were injected with the same organism in doses down to 0.5 cc All showed at necropsy, hemorrhages in the gastric mucosa

CASE 3—H. A. A., aged 44, a business man, had several gastric hemorrhages, in December, 1922 For six months previous to this, he had had indigestion, consisting principally of a feeling of fulness after eating A diagnosis of duodenal ulcer was made Several teeth were extracted at this time Rest in bed for one month, milk diet and alkalis entirely relieved the symptoms The patient states that he still has indigestion, at times, for which he takes soda

Roentgenograms, in June, 1924, showed one tooth of questionable vitality and one pulpless tooth with little roentgenographic evidence of infection At the site of extraction of the upper left first bicuspid and first molar, some filling material remained, and the surrounding bone showed evidences of infection (Fig 3, C) The two teeth were extracted and the infected bone curetted Cultures in deep tubes of glucose brain broth agar showed a short chain streptococcus in all

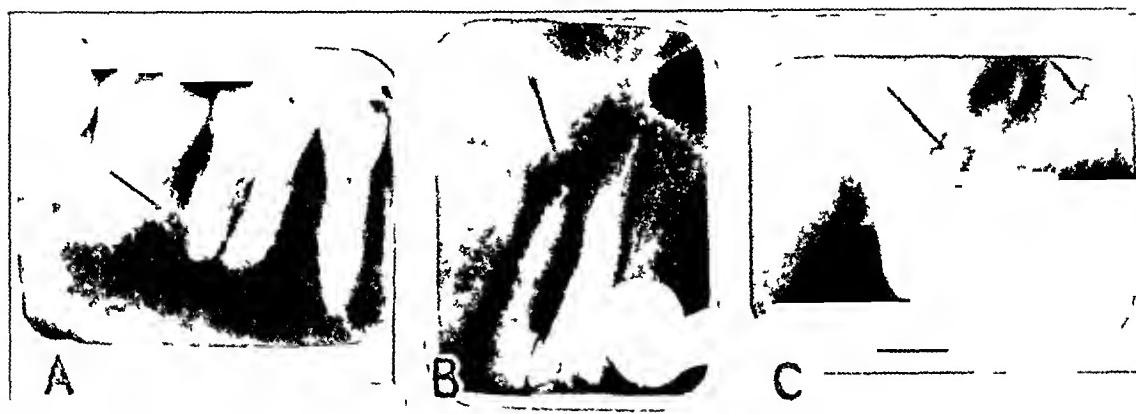


Fig 3—*A*, first molar, showing no roentgenographic evidence of infection The culture showed an anaerobic streptococcus, which produced gastric lesions on intravenous injection (Case 9) *B*, cuspid and first bicuspid, Case 2, both showing evidence of infection Both teeth showed a profuse growth of organisms on culture The organisms from the cuspid tooth produced no gastric lesions, while those from the cuspid caused very marked lesions (Fig 2, B) *C*, small bits of gutta percha remaining at the site of extraction of infected teeth, surrounded by an area of infected bone (Case 3) A pure culture of green producing streptococci was grown from the curettings which, on injection, caused the lesion shown in Figure 4, *B*

Animal Inoculation—Two rabbits were inoculated with the mixed broth cultures One rabbit was dead the following morning and showed many hemorrhages in the duodenum The second rabbit was killed This one also showed many hemorrhages in the first third of the duodenum without lesions elsewhere (Fig 4, *A*)

In order to determine whether the area of infected bone might play a part in the causation of the peptic ulcer, one rabbit was injected with 5 cc of the broth culture from this area alone At necropsy, twenty-four hours later, the duodenum showed massive hemorrhages (Fig 4, *B*) There were no other lesions

CASE 4—S. T., aged 50, a coal dealer stated that he had had three attacks of pain in the epigastrium coming on one or two hours after meals The pain occurred also at night, and was relieved by food or soda There was

no nausea or vomiting. The present attack began three weeks before admission. He had noticed some irregularity of the heart for ten years. The previous history was negative, except for occasional attacks of rheumatism and gall-stone colic ten years before. The tonsils had been removed.

On examination, the heart action was persistently irregular, the blood pressure was 120, the lungs and abdomen were negative. There were many crowned teeth, the urine examination was negative, the hemoglobin was 80 per cent, and white corpuscles totaled 14,000. The fluoroscopic examination showed forceful peristaltic waves and a deformed duodenal cap. A diagnosis of duodenal ulcer and auricular fibrillation was made.

Animal Inoculations—Six rabbits injected with the broth culture from the lower teeth and nine upper teeth showed no lesions anywhere when killed, twenty-four hours after injection. One rabbit injected with the mixed cultures

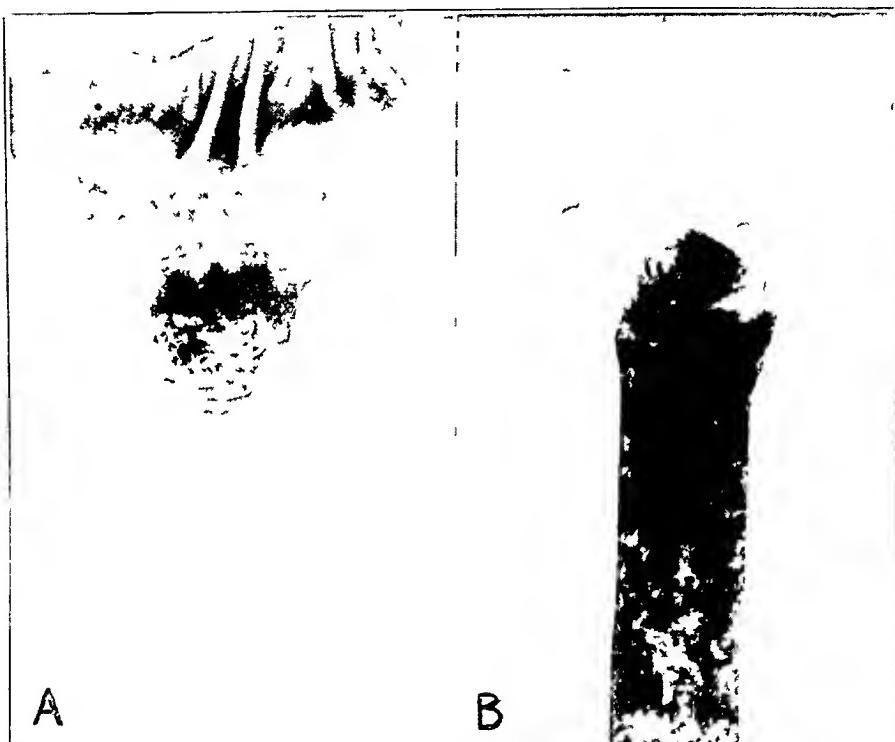


Fig. 4.—A, lesion in duodenum following the intravenous injection of mixed cultures, Case 3, B, extreme involvement of duodenum following the injection of streptococcus from area of residual infection (Fig. 3, C)

of streptococci from the upper left central, lateral and cuspid showed about 100 hemorrhages in the first third of the duodenum and a few hemorrhages in the wall of the pyloric end of the stomach. The only other lesions found were a few small areas of necrosis in the muscle.

Within ten days after extraction, the heart action returned to normal and has remained so. The stomach symptoms also cleared up.

CASE 5—G. W. P., aged 47, a merchant, complained of abdominal pain of ten years' duration. He stated that he had had attacks of "dyspepsia" for eight or ten years. For six months, he had suffered from an aching pain in the epigastrium occurring two to three hours after meals. He was occasionally awakened at night. The pain was relieved by food or soda. He had been on a milk diet for six months with relief from pain, except at night.

The general examination was negative. The Wassermann reaction was negative. The blood and urine examinations were negative. Roentgenographic examination showed a duodenal ulcer. Gastric analysis showed free hydrochloric acid, 60 per cent acidity, and total acid, 100 per cent acidity. Operation, March 26, 1924, confirmed the diagnosis of duodenal ulcer. The appendix was removed, and a posterior gastro-enterostomy done.

Roentgenograms of the teeth showed several teeth with bone absorption around the root tip and an area of residual infection.

Animal Inoculations—Two rabbits were injected with a culture from the residual area. One showed some lesions in the kidney medulla. The other showed hemorrhage and ulceration in the pyloric end of the stomach, and a few hemorrhages in the lumbar muscles. Two rabbits injected with the culture from the tooth showed lesions in the kidney medulla of both and purulent fluid in the joint of one.

CASE 6—J. A. L., aged 62, a lawyer, complained of headache, a tired feeling, and a dull ache in the epigastrium. He stated that the headache had troubled him for a number of years. The first attack of stomach trouble had occurred in 1908, and was characterized by pain in the epigastrium coming on one hour after meals. The pain was relieved by taking food. He had had numerous attacks and was just recovering from one when first seen. There had been no nausea or vomiting. The general physical examination was negative. The blood pressure was 125 systolic, 80 diastolic, the red cells totaled 5,120,000, the white cells, 8,100, and the hemoglobin was 100 per cent. The urine showed albumin and a few granular casts. The specific gravity was 1.035. The blood urea nitrogen was 29.5 mg per hundred cubic centimeters, and the phenolsulphonephthalein test showed an excretion of 53 per cent in two hours. A diagnosis of chronic nephritis, cholelithiasis and duodenal ulcer was made.

Several infected teeth were extracted. Cultures showed only a green producing streptococcus.

Animal Inoculations—Two rabbits were injected with the mixed cultures. One animal died the night following the injection and, at necropsy, showed no localized lesions. The other rabbit was killed three days after injection. There were many hemorrhages in the pyloric end of the stomach. There also was purulent fluid in the joints, some areas of necrosis in the voluntary muscle, numerous areas of necrosis in the muscle wall of the pyloric end of the stomach, abscesses in the medulla of the kidney and involvement of the heart muscle and pericardium.

CASE 7—R. McC., aged 47, a clerk, complained of pain in the epigastrium. He had always been well except for an attack of influenza, in 1918. The epigastric pain had occurred intermittently for five years. It came on about two hours after meals, and was relieved by food or soda. The physical examination was negative, except for tenderness in the epigastrium and numerous crowned teeth. The urine was negative. The blood count showed 4,200,000 red cells, 9,000 white corpuscles and 90 per cent hemoglobin. The gastric analysis showed a total acidity of 95. A clinical diagnosis of duodenal ulcer was made. Feb 14, 1923, four pulless teeth were extracted.

Animal Inoculations—Two rabbits were injected with the mixed cultures. One died, two days later. There was some pericorneal injection. The necropsy showed many hemorrhages in the first third of the duodenum. The second rabbit was killed, two days after injection. One large hemorrhage in the mucosa of the fundus of the stomach was found. There also were a purulent arthritis and abscesses in the kidney medulla and myocardium.

CASE 8—G. B., aged 72, a financier, was first seen following a copious gastric hemorrhage. He was in an excellent state of nutrition, was very active,

and had never been ill previously. The present illness had begun, shortly before, with a fainting attack followed by the vomiting of a large amount of blood. He also passed blood in the stools. The roentgenographic examination of the stomach showed no abnormality. The Wassermann reaction was negative. The physical examination was negative, except for the evident anemia and some tenderness over the spleen. The blood count showed 2,100,000 red cells, white corpuscles and 42 per cent hemoglobin. The patient made a gradual recovery without further gastric symptoms.

A roentgenogram of the teeth showed four pulpless molar teeth, only one of which had an area of bone absorption around the root tip.

Animal Inoculations.—Cultures from the upper right first and second molars showed, in deep tubes of glucose brain broth agar, a very large number of colonies of a gram-positive diplococcus. One rabbit injected with the culture from the first molar showed no gastric lesion. Two rabbits were injected with the culture from the second molar. One showed many hemorrhages in the mucosa of the stomach. There were no other lesions, except a few hemorrhages in the myocardium. The second rabbit showed no lesions. The lower

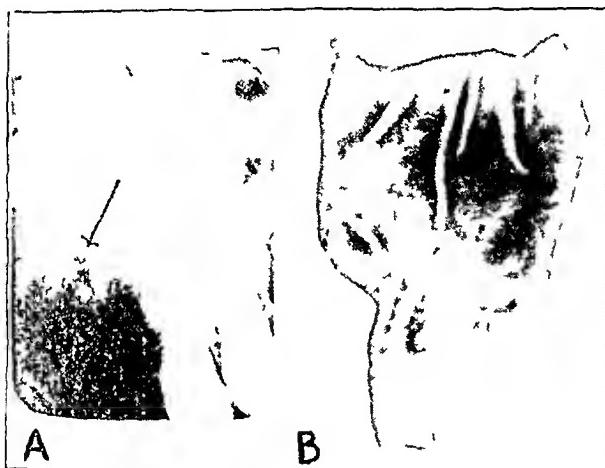


Fig 5.—A, area of infected bone at the site of extraction of infected tooth, the culture from which showed a streptococcus, B, ulcers in stomach of rabbit produced by the intravenous injection of the organism recovered from the area in A, Case 10.

right second molar and the upper left first molar were extracted several days later. Both showed, on culture, a profuse growth of diplococci. Two rabbits were injected intravenously with the mixed cultures. Both, at necropsy two days later, showed hemorrhage in the first third of the duodenum with no lesions elsewhere.

CASE 9—C. T. C., aged 26, a medical student, complained of a duodenal ulcer. He had always enjoyed excellent health before his present illness, except for some rheumatic pains which had been relieved by tonsillectomy. The present trouble began soon after the tonsillectomy, in March, 1923, with epigastric pain, occurring before meals and about two hours after meals. The pain was relieved by food or alkalis. A fluoroscopic examination, in December, 1923, showed definite signs of a duodenal ulcer. Under alkalis and dietetic treatment, he improved.

The dental roentgenograms revealed three pulpless teeth, none of which showed roentgenographic evidence of infection. March 19, two of the teeth

were removed. Two rabbits injected with the broth cultures showed no lesions anywhere. Several days later, the left lower first molar (Fig. 3, A) was extracted. A pure culture of a short chain streptococcus growing out in the anaerobic portion of the culture tube was obtained. Two rabbits were injected. Both, at necropsy, showed hemorrhage and ulceration in the pyloric end of the stomach. There were also necrosis in the muscles, vegetations on

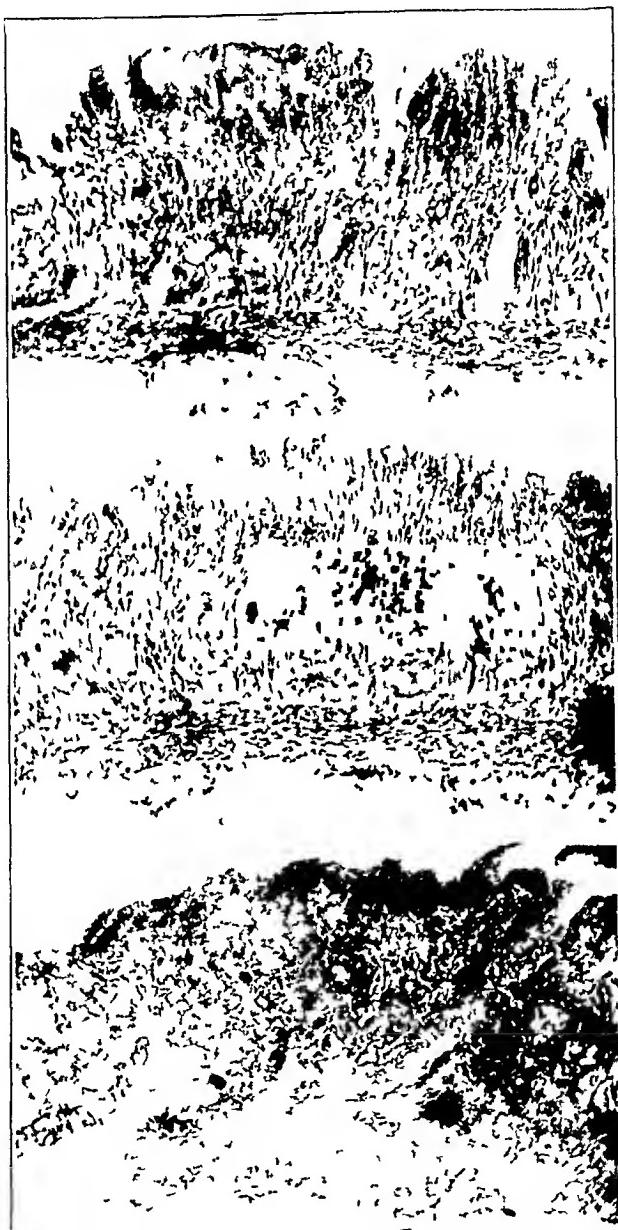


Fig. 6.—Peptic lesions produced by the intravenous injection of bacteria from dental infection above and middle, stomach, below, duodendum. There is marked hemorrhage, necrosis of the surface and polymorphonuclear infiltration

the heart valves in one, and purulent fluid in the joints, cortical kidney abscesses, peritoneal injection and white streaks in the muscle of the other

CASE 10—E. W. M., aged 25, an elevator constructor, complained of pain in the stomach, stating that he had had an attack of epigastric pain lasting several weeks, in 1921. He had never had any other serious illness. His present attack had begun six weeks before admission, and was characterized

by a gnawing pain in the epigastrium coming on before meals and relieved by food and soda. He was kept awake at night by the pain.

The patient was a well nourished, athletic individual. The tonsils had been removed. The physical examination was essentially negative. The blood count showed 3,584,000 red blood cells and 11,900 leukocytes. The stool was negative for occult blood. The meal showed 18 per cent acidity, free hydrochloric acid and 60 per cent acidity total hydrochloric acid at the end of an hour.

The dental roentgenograms showed three pulpless teeth all presenting evidence of infection.

Animal Inoculations—Two rabbits each were injected with the cultures from the left lower central incisor, upper left cuspid and upper left first molar. Two were killed, and one died twenty-four hours after injection and showed no lesions at necropsy. Three were killed forty-eight hours after injection. One showed hemorrhage in the first part of the duodenum and lesions in the kidney medulla. One showed only muscle lesions, the other, muscle lesions, an ulcer in the pyloric end of the stomach, and slight joint involvement.

One month after the first teeth were extracted, an area of infected bone in the region of the upper right cuspid was curetted. A profuse growth of streptococci was obtained in the deep agar tube. One rabbit was injected with broth culture. At necropsy, two days later, there were multiple hemorrhages and beginning ulceration in the pyloric end of the stomach. There also were abscesses in the kidney medulla, hemorrhagic areas in the muscles and the myocardium, and small vegetations on the mitral valve.

CASE 11—Mrs. G. E. S., aged 33, a housewife, stated that her stomach trouble had begun, ten months before, with pain in the abdomen, occurring about one-half hour after meals, and also a gnawing pain two to three hours after eating. She was often awakened at night with the pain. Her tonsils had been removed, in 1917. She had had pneumonia with empyema, in 1904, but had been well for ten years preceding the present illness.

The general physical examination was negative. The red blood cell count was 4,312,000, the hemoglobin 90 per cent, and the white count, 8,100. The gastric test meal showed free hydrochloric acid 8 per cent acidity and 29 per cent total acidity.

The dental roentgenographs showed one tooth, the left upper first bicuspid, of questionable vitality. The left upper second bicuspid was pulpless, but showed no area of rarefaction of bone at the root tip. There was an area of residual infection at the site of extraction of the left lower first molar. The two bicuspids were cultured together and showed a profuse growth, in pure culture of a green producing streptococcus. A pure culture of the same organism also was obtained from the area of infection.

Animal Inoculations—Two rabbits were injected with the mixed broth cultures. One showed, at necropsy, hemorrhage and erosion in the pyloric end of the stomach, medullary lesions in the kidney and purulent exudate in the joints. The other showed numerous ulcerated hemorrhagic areas in the pyloric end of the stomach, a purulent arthritis, lesions in the kidney medulla and a few areas of infection in the muscles.

CASE 12—I. A. P., aged 50, a housewife, gave a typical history of duodenal ulcer, with recurrent attacks over a period of fifteen years. The epigastric pain was dull gnawing in character, and came on two to three hours after meals and during the night, the present attack had begun six weeks previously.

The patient was rather obese. There was tenderness in the epigastrum. The gastric analysis showed free hydrochloric acid 27 per cent acidity, and total acid, 51 per cent acidity. The stool was negative for occult blood. The blood count was normal.

The roentgenogram showed two pulpless teeth, the left lower first and second bicuspids. A culture in the deep agar tube of the first bicuspid showed 50 colonies of a green producing streptococcus, the second bicuspid, a profuse growth of a similar organism.

Animal Inoculations.—Two rabbits were injected with the mixed cultures from the two teeth. One, at necropsy, showed no lesions, the other, a very marked involvement of the muscle wall of the pyloric end of the stomach extending through to the mucosa. There also was purulent fluid in the joints, lesions in the kidney medulla and some areas of necrosis in the voluntary muscles.

EXPERIMENTAL MORPHIN POISONING *

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The incentive to the experimental work described here in detail was provided by the investigations of Valenti,¹ in 1914. The work was actually begun in 1920 but, owing to circumstances over which we had no control, it was discontinued and resumed only in February, 1923.

A great deal of investigation has been carried on with morphin poisoning, and an excellent résumé has been presented by Du Mez.² It is clear that the opinion regarding the action of this alkaloid and its manner of destruction, or at least its alteration, in the animal body is a matter of considerable dispute.

At the present time and, as a matter of fact, ever since the Harrison Act went into effect, the problem of drug addiction and of handling addicts has been of sufficient gravity to attract the attention of a large number of investigators. On account of the conditions brought about by the enforcement of this act, interest has been renewed in the scientific investigations into the ultimate cause of morphin addiction. In general, this experimental work has been carried on with the lower animals being used as subjects. In many respects, the parallelism between morphin poisoning under experimental conditions in dogs, rabbits, guinea-pigs, rats or mice and that in the human being is by no means complete. This is notably the case during the withdrawal period, which presents the most characteristic symptoms in the human being. With animals, particularly with dogs, so far as our experiment goes, this does not hold true in any sense of the word. The popular periodicals have drawn considerable attention to the fact that Valenti succeeded in producing canine addicts presenting all the characteristics of morphin poisoning and even showing a desire for repeated injections when morphin had been withdrawn for some time. In other words, the overzealous but

* From the department of hygiene and public health, Tulane University of Louisiana School of Medicine

1 Valenti Arch f exper Path u Pharmakol, March 5, 1914

2 Du Mez, A G Increased Tolerance and Withdrawal Phenomena in Chronic Morphinism, J A M A 72 1069 (April 12) 1919

inaccurate and unscientific writer of the articles adopted Valenti's conclusions to his own ends, which were certainly not justified, as is seen when we refer to the work itself.

Our original plan was conceived with several objects in view. Primarily, we were interested in determining whether arrhythmia or other disturbance in heart function was produced during the abstinent period of habituated dogs. It was expected that the electrocardiograph would confirm or refute this point without the sacrifice of the animal. Secondly, it was anticipated that in the event arrhythmia or other cardiac irregularity was found to occur, the serum from such animals was to be injected into normal dogs, in order to confirm the second step of Valenti's work, viz., that some substance circulates in the blood stream which is responsible for the heart disturbances. Thirdly, it seemed desirable to use the serum of dogs containing this toxic substance which undoubtedly would be of a protein nature, and by injecting it into normal animals produce an antibody. It was hoped that this antibody would immediately relieve the cardiac disturbances in the withdrawal period. We now know, from the work of Pellini and Greenfield,³ that this substance does not exist.

ELECTROCARDIOGRAMS

For our purpose, three healthy dogs were selected, weighing respectively 16 pounds, 3 ounces (7,349 gm.), 13 pounds, 4 ounces (7,377 gm.), and 22 pounds, 1 ounce (7,292 gm.). The injections were begun, March 1, 1923, with an initial dosage of 20 mg. The dosage was gradually increased until, July 20, each dog was receiving 650 mg., or 10 grains daily. All dogs were therefore subjected to the action of morphin for a period of four months and twenty days. Dog 1 received a total of 54.2 gm. (833.5 grains), Dog 2 received 51.756 gm. (798.6 grains), and Dog 3 received 53.744 gm. (829.3 grains). The last dose was given the afternoon of July 20. The next day, an electrocardiogram was made from each dog. This was repeated July 24, and again July 26.

Twenty-four hours were allowed to elapse following the last administration of the drug in order to promote the development of the same conditions under which the dog existed while being morphinized. It was believed that this would be sufficient time for the absorption of the dose from the subcutaneous tissue, and would not be too long a period for the initial symptoms to establish themselves. Forty-eight hours (the third day) from the last dosage should have been sufficient time for the

³ Pellini, E. J., and Greenfield, A. D. Narcotic Drug Addiction, Arch Int Med 33:547 (May) 1924.

withdrawal symptoms to develop. They should reach a maximum on the fifth day, i.e., July 25, when the dogs would probably have eliminated or destroyed all the morphin which had been injected. We could not observe in these electrocardiograms any signs of arrhythmia or variability attributable to prolongation of the abstinence period, and certainly arrhythmia or serious cardiac disturbances would have been evident with such a sensitive instrument had they been present. It is true that in Dog 3 the third electrocardiogram showed a reversal of the T wave (Figs. 1, 2 and 3). This evidence did not warrant, nor would circumstances permit, our carrying out the other steps of our program.

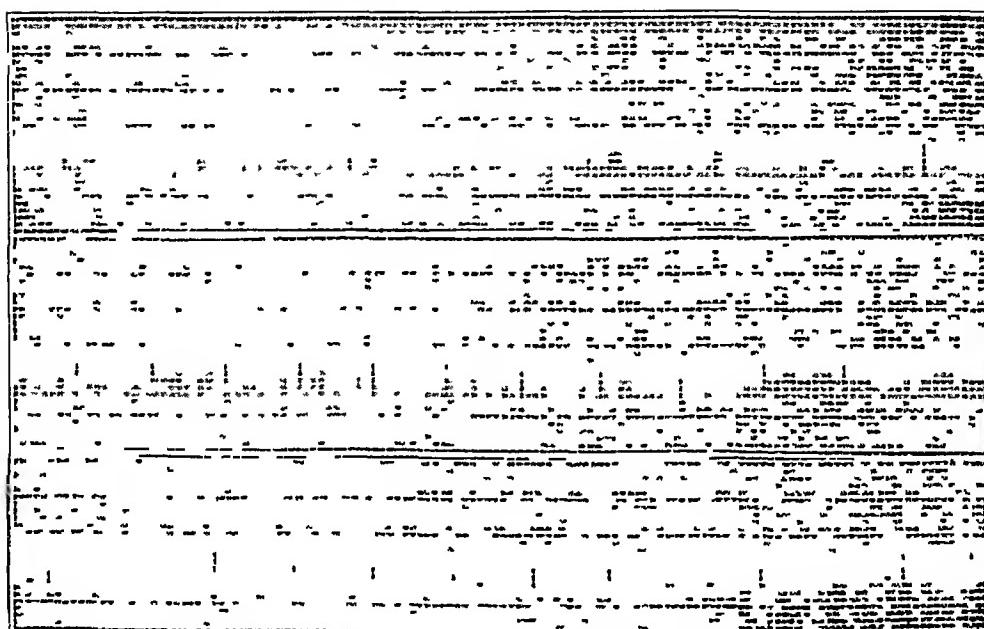


Fig. 1—Lead III, Dog 1, July 21, 23 and 25, 1923, during abstinence period.

July 31, by an oversight, each dog again received an original dose of 10 grains, or 650 mg., and the next day, August 1, Dogs 1 and 2 were dead, while Dog 3 barely survived. Injections of Dog 3 were continued up to Jan 29, 1924, the dog at times receiving as high as 2145 gm (33 grains) in a single dose. For some unknown reason, it died on the night of January 29, when we were preparing to make another series of electrocardiograms. This dog had received altogether, between March 1, 1923, and Jan 29, 1924, 148.554 gm (2,755 1 grains) of morphin sulphate.

We are well aware of the fact that dogs can survive remarkably large doses of morphin, nevertheless, during previous experiments, we have found it very advisable to begin with a very small dosage and to increase it gradually until what seems to be a satisfactory period has

been overcome. The amount could then be increased quite rapidly. One is not always successful even with small doses, as we learned from experiments in 1921, when three dogs were killed with comparatively small amounts of morphin repeated over a period of approximately thirty days. It seems possible that death was due to pyelitis, for which the constipated condition of the animals was directly responsible.

Never, at any period of the administration, have we been able to observe a dog showing a desire for the alkaloid comparable to that exhibited by human beings. On the contrary, almost invariably there was a reaction following each injection, and the dogs would complain bitterly, unless stuporous from the previous dose. Neither could we

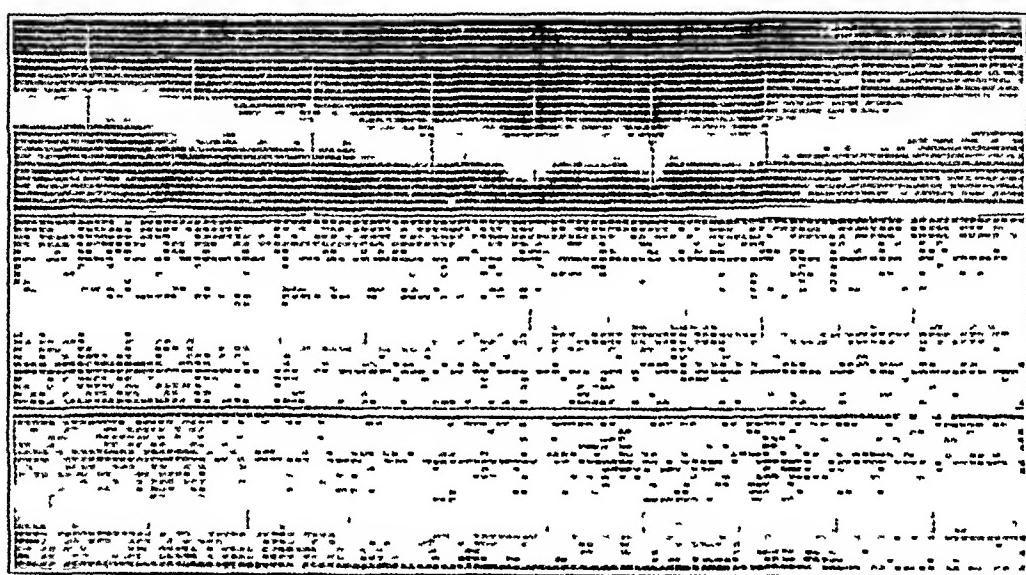


Fig 2.—Lead III, Dog 2, July 21, 23 and 25, 1923, during abstinence period

observe any nervous symptoms or signs of extreme agitation during the abstinence period. This refutes completely the popular statement that a dog could be converted into an addict and act in the same manner as a human being would act. We found no evidence that such was the case.

BLOOD EXPERIMENTS

As Morgenroth⁴ and a number of other investigators have apparently demonstrated the capacity of the red cells to absorb quinin from the plasma, it was thought possible that the same phenomenon might hold true for another alkaloid, morphin. Furthermore, the hypothesis that the red corpuscles destroy or alter morphin so as to render it inactive is not altogether untenable.

⁴ Morgenroth. *Deutsch med Wochenschr* 44: 961, 988, 1918.

For our purpose, the blood of a dog which had received daily injections of morphin sulphate from Feb 1 until June 19, 1924, was used. These injections began with 32 mg (one-half grain), and increased to 650 mg (10 grains), the latter amount being administered for more than six weeks. The dog received a total of 26,378 gm (407 grains) during the entire period.

June 29, 10 c.c. of blood was removed from the heart and defibrinated, the serum and blood cells were separated, and the latter thoroughly washed with physiologic sodium chlorid solution. Blood cells, serum and controls, with varying quantities of morphin, were arranged according to the scheme given in the accompanying table.

Arrangement of Blood Cells, Serums and Controls in Experiments with Morphin

	Serum	Saline Solution	Red Cells	Morphin Solution*
Row 1	0.5 c.c.	0.5 c.c.		0.1, 0.2, 0.3, 0.4 c.c.
Row 2	0.5 c.c.		0.5 c.c.	0.1, 0.2, 0.3, 0.4 c.c.
Row 3	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.1, 0.2, 0.3, 0.4 c.c.

* One cubic centimeter contained 65 mg (1 grain) of morphin sulphate.

The tubes were allowed to stand at 37 C, for two hours, in a water bath and were then placed in the icebox over night.

The method used in extracting the morphin was that of coagulation with heat and a faint excess of acetic acid, the filtrate was then evaporated from the coagulum and the residue extracted repeatedly with Prolli's mixture (ether, 65 parts, alcohol, 5 parts, and strong ammonia, 1 part). The red cells in Rows 2 and 3 were, of course, separated from the serum and saline and thoroughly washed until the washings showed no trace of alkaloid. They were then coagulated, filtered and extracted.

The results were entirely negative so far as absorption by the red cells was concerned. With the exception of the very faintest traces in two tubes in Row 2, of 0.3 c.c., and in Row 3, of 0.4 c.c., which were doubtful, no morphin could be detected in the blood cells themselves. It was readily separated from the serum and saline with which the cells had been mixed.

PROTECTIVE SUBSTANCES IN THE BLOOD

The results obtained by Hirschlaaff⁶ indicated, at least to himself, that an antibody was formed when morphin, in gradually increasing doses, was injected into animals. His tables show that in many cases he succeeded in saving the lives of animals by injecting them with

serum from a morphinized rabbit He also tried his serum on an acute case of opium tincture poisoning, and the person was apparently saved by its action

Hirschlaff cites the work of Gioffredi, who obtained similar results with cats and a dog The serum prepared by Gioffredi is said to have saved a dog after double the lethal dose of morphin

Morgenroth⁶ repeated Hirschlaff's experiments with both rabbit and goat serum He points to numerous fallacious deductions of Hirschlaff, notably the incorrect lethal dose for mice and the distinct protective influence of rabbit serum Pellini and Greenfield⁷ have shown that no protective substance exists in the serum after either human or canine morphin poisoning

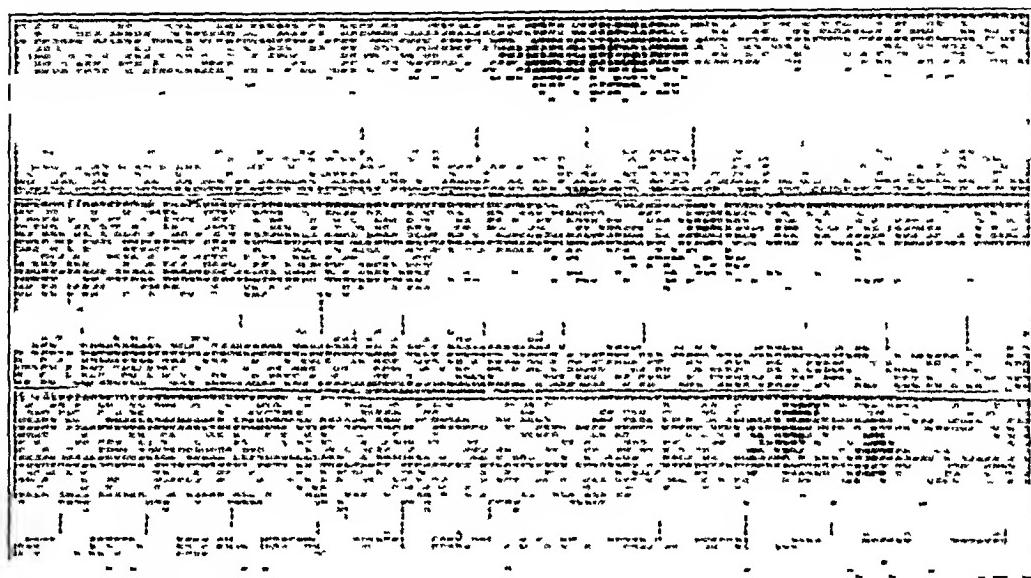


Fig 3—Lead III, Dog 3, July 21, 23 and 25, 1923, during abstinence period

With these and similar observations in mind, we decided to test the protective action of defibrinated blood drawn from Dog 4 on a normal animal

Accordingly, June 21, i.e., five months and twenty days from the beginning of the experiment and after two days of morphin abstinence, 50 c.c. of blood were drawn from the heart, under sterile precautions, and defibrinated

To 10 c.c. of this blood were added 195 mg (3 grains) of morphin sulphate in solution This was allowed to stand on ice for twenty-four hours, and the entire amount, 13 c.c., was injected subcutaneously into

6 Morgenroth Berl klin Wchnschr 40 471, 1903

7 Pellini, E J, and Greenfield, A D Formation of Protective Substances Against Morphin, Arch Int Med 26 279 (Sept) 1920

a normal dog, weighing 20 pounds, 5 ounces (9,214 gm) One day prior to this injection, it was determined that a control of 10 cc of untreated blood produced no reaction

The morphin blood mixture was administered at 3 15 p m , June 23 In about five minutes, vomiting occurred, with moderate salivation Then, gradually, the animal lapsed into a stuporous condition, from which it could be aroused with difficulty only to subside immediately on the floor

At 9 30 a m , June 24, the animal was still drowsy and stuporous, but less so than the night before June 25, the animal had completely recovered The absorption at the site of injection was very slow, and the wheal still persisted, even though the morphin symptoms had disappeared We could not conclude from our observations that the blood offered any protection whatever or mitigated the symptoms in the least

ALTERATION OF MORPHIN IN VIVO

A number of investigators, notable among whom are Faust, Cloetta and Marmé,⁸ have held that morphin was converted by the body into the oxidation product variously called oxydimorphin, dihydromorphin and pseudomorphin Some workers claim to have detected the presence of this substance in the excreta of animals poisoned with morphin, one (Marme) holding that the abstinence symptoms were caused by it According to Du Mez and Valenti, Albanese proved that the livers of morphinized dogs were capable of destroying, or at least of altering, the constitution of morphin

Another point in this connection was the supposition of Valenti that morphin was destroyed soon after injection because he failed to find a trace of the alkaloid in 50 c c of blood four hours after injecting 40 c c of 5 per cent morphin solution (2 gm) into the external jugular vein

The experiment decided on was intended to, at least partially, reduplicate this work Dog 4, after forty-eight hours of abstinence, was selected for this purpose, and the work was carried out under ether anesthesia For the sake of clarity, this experiment may be divided into three parts

(a) Six hundred and fifty milligrams (10 grains) of morphin sulphate was injected into the portal circulation About eight minutes later, 45 c c of blood was removed directly from the heart

(b) The hepatic and portal veins were ligated, and the liver was removed The liver was connected with a cannula and perfused with

⁸ Acquired Tolerance of Morphin, editorial, J A M A **66** 657 (Feb 26) 1916 Faust, E S Arch f exper Path u Pharmakol **44** 217, 1900 Cloetta, M Ibid **50** 453, 1903 Marme Deutsch med Wchnschr **14** 197, 1883

distilled water through the portal system until the wash water amounted to approximately 1,000 c.c. and gave no alkaloidal reaction.

(c) The liver was ground up fine and 325 mg (5 grains) of morphin in solution was mixed thoroughly with 200 gm. The mixture was allowed to stand in the icebox for forty-eight hours.

RESULTS

The 45 c.c. of blood (a) was evaporated to dryness. The residue was ground up fine and repeatedly extracted with hot alcohol containing ammonia. This residue was moistened with hydrochloric acid, filtered and again evaporated. A test for morphin with Froehde's reagent was faintly positive. There was a faint greenish tinge to the coloration. Both Mayer's alkaloidal reagent and iodin potassium iodid solution gave positive reactions.

The wash water obtained by perfusing the liver (b) was coagulated with dilute acetic acid and heat, and, after being filtered, was evaporated to dryness. The residue was extracted repeatedly with alcohol and ammonia, evaporated and weighed. The yield was 48 mg. This was acidified with hydrochloric acid and carefully evaporated. Tests for morphin with Froehde's reagent and formaldehyd sulphuric acid were positive with a tendency to turn green, said to be a characteristic test for oxydimorphin. Obviously, the morphin had been changed in the liver capillaries and apparently much was destroyed, unless it had succeeded in gaining access to the general circulation before the connection was ligated.

The liver morphin mixture (c) yielded the best and the most interesting results, besides apparently confirming the work of Albanese already mentioned.

This mixture was coagulated with heat and acetic acid, filtered with a Buchner funnel, and the filtrate evaporated to dryness in the water bath. The residue, which was considerable, was repeatedly extracted with hot ammoniacal alcohol. The exhaustion of the residues from repeated extraction was completed three times, the final yield being soluble in hot alcohol and insoluble in water. The last extraction, when evaporated, yielded a residue which, while colored, was obviously nearly pure, since it was almost entirely crystalline. It could be divided, by treating with Prollius' mixture, into two parts, which together amounted to 147 mg of morphin, equivalent to 319 mg, or 4.9 grains, of crystalline morphin sulphate.

Both parts gave strong reactions for morphin with Froehde's reagent and with formaldehyd sulphuric acid, as well as Pellagri's reaction. However, the larger portion of the two, when treated with both

Froehde's reagent and formaldehyd sulphuric acid changed to a green color in a very short time, which true morphin does not. The two portions combined gave a faint reaction for apomorphin, which was to be expected since the residue had been treated with hydrochloric acid. The amount apparently was negligible.

It was very desirable to note the effect of this substance on a normal dog. Accordingly, a solution was made and injected subcutaneously into the one that had recovered completely from the morphin blood mixture. There undoubtedly was more than the equivalent of 4 grains (0.26 gm.) of morphin sulphate remaining after the tests had been made, so it was reasonable to expect signs of morphin poisoning had this been the unchanged drug.

The injection was given at 12:40 p.m., June 26, and aside from vomiting twice, the animal had no symptoms whatever. The dog appeared perfectly normal, and at no time did it show a tendency to develop lethargy and stupor, which is a characteristic effect of morphin. Obviously, this was a substance which, in the main, accorded with morphin so far as the chemical tests were concerned, but which lacked the toxic qualities of the alkaloid. The National Standard Dispensatory (Edition 3) states that the development of a green color with the formaldehyd sulphuric acid test and with Froehde's reagent is the feature which distinguishes pseudomorphin or oxydimorphin from unchanged morphin. It does not state whether this color is produced immediately or whether it develops from the reddish purple, on standing, as in the latter case.

As a further control and to test the susceptibility of this dog to morphin, 130 mg (2 grains) of morphin sulphate were injected at 9:15 a.m., June 27.

The objective symptoms which developed, within a short time after the injection, consisted of salivation, rapid breathing and lethargy. The dog became stuporous and indisposed to move, the general effect, however, being less than that following the injection of the blood containing 195 mg (3 grains) of morphin, June 23. While it had recovered almost entirely, June 28, there was sufficient proof that it reacted very definitely to the small dose administered.

CONCLUSIONS

While the work is far from being as complete and convincing as it was expected it would be at the outset, nevertheless, it is believed that certain tentative conclusions are justified.

1. The electrocardiograph does not show the cardiac disturbances which we were led to expect would occur in accordance with Valenti's

observations While the highest dosage in any one day was less than that administered by Valenti to his animals, the period was much longer and the amount of morphin was either equal to or several times greater than he used, so this could hardly have been a disturbing feature in the experiment

2 The fact that the immunity developed by increased dosage disappears very rapidly is shown by the fact that two out of three dogs succumbed, and one narrowly escaped, when the accustomed amount of morphin was given after an abstinence of only ten days (July 21-31, 1923) This fact, which we know also holds true for human addicts, argues against the presence of an antibody

3. Whole blood does not measurably protect a normal animal, even though the blood has been given ample time to alter, combine or destroy the morphin Apparently, the symptoms are protracted, probably owing to the slower absorption of the protein alkaloid combination

4 Morphin, unlike quinin, is not abstracted from serum by the red cells These apparently play no part whatever in protecting the body from the poisonous action Whether the serum produces any alteration in the morphin molecule, we do not know, that it was not destroyed is shown by the recovery from the serum

5 Morphin injected into a portal branch passes rapidly into the general circulation and can be obtained from the blood a few minutes after the injection It is probably altered, because the identification tests, while faint, show a greenish tinge This is also the case with morphin which remains behind in the liver capillaries and which is recovered by perfusion with distilled water

6 Liver tissue alters morphin very markedly and the resultant change in the structure is probably similar to that observed by Albanese Whatever this substance may be, and we are by no means certain that it is entirely pseudomorphin, it is, at any rate, innocuous, and produces no symptoms of morphin poisoning when injected into a susceptible animal

7 It is highly probable that the liver is at least one of the organs, if not the principal one, involved in the destruction of morphin

ACTION OF DIGITALIS IN THE PRESENCE OF CORONARY OBSTRUCTION

AN EXPERIMENTAL STUDY *

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The present investigation was undertaken to determine whether interference with the coronary circulation has any effect on the tolerance of an animal to the digitalis bodies¹

There has long been a certain hesitation to administer digitalis to patients with heart failure associated with disorders of rhythm similar to those arising from excessive digitalization. Because of the striking similarity between the cardiac disturbances resulting from diphtheria and those from large doses of digitalis, McCullough² recommended that the drug be withheld in this disease. The existence of such disorders as premature beats, coupling, various degrees of heart block and pulsus alternans has been taken by some as a contraindication to the use of digitalis, or, at least, as an indication for especial caution in its administration. It has seemed logical to assume that the occurrence of these abnormal phenomena implied a predisposition in the heart to their development through the digitalis bodies that are capable of producing them in the normal heart. But evidence appeared from time to time that challenged this supposition. Bie and Schwensen³ recorded the effects of digitalis in two patients with diphtheria who had developed a "complex irregularity" of the heart, which was fatal in all of ten patients reported by one of the authors previously. The administration of digitalis in full doses to both patients was followed by the disappearance of the irregularities. One recovered entirely, the other developed further disturbances of rhythm, and died in several days. Bush⁴ reported some experiments from which he deduced that diphtheria toxin rendered the heart of the dog and of the frog more susceptible to ouabain, but his data do not warrant his conclusions. Wenckebach⁵

* From the department of pharmacology of Cornell University Medical College

1 The words "digitalis" and "ouabain" are employed interchangeably in this paper, although only ouabain was used for injection.

2 McCullough, H. On the Administration of Digitalis to Children with Diphtheria, South M J **14** 110 (Feb.) 1921

3 Bie, V., and Schwensen, C. The Effect of Digitalis in Two Cases of Arrhythmia in Diphtheria, J Infect Dis **30** 308 (March) 1922

4 Bush, A D. Drug Action as Modified by Disease Toxins, I, Ouabain Vs Diphtheria Toxin, J Pharmacol & Exper Therap **13** 55 (April) 1919

5 Wenckebach, K F. The Effects of Digitalis on the Human Heart, Brit M J **2** 1600, 1910

observed that troublesome extrasystoles, which had persisted for a long time, disappeared after digitalis medication. Edens and Huber⁶ recorded similar observations. While pulsus alternans has been seen in a few cases to follow overdigitalization, digitalis administered to patients with pulsus alternans has sometimes abolished it.⁵ Christian⁷ observed that, in pulsus alternans, digitalis frequently produced good results, yet he warned that, in view of the great impairment of the myocardium in this condition, the likelihood of improvement was much reduced and to push digitalis in such a case might do much damage. Windle,⁸ on the other hand, observed no harm from digitalis in 100 patients with pulsus alternans, though he found that frequently the disparity between the beats was diminished or abolished and that the general symptoms were improved. He recommended the use of digitalis until the onset of vomiting or coupled rhythm.

The discrepancies in clinical reports may be partly explained by the complex nature of digitalis action. For example, small doses stimulate the vagus and diminish the excitability of the heart, large doses may increase the irritability of the heart by direct action on the myocardium. Thus, small doses may abolish extrasystoles, large doses produce them.⁵ It also seems more than probable that a certain irregularity of the heart, being symptomatic of widely different conditions, as, for instance, diphtheria, on the one hand, and arteriosclerotic heart failure, on the other, may show as wide variations in response to digitalis. In one instance, it is conceivable that the drug will have no effect or even, in some cases, exaggerate the disorder; in another instance, with improvement in the heart action, the irregularity may disappear.

In this connection, Windle⁸ has called attention to the fact that alternation of the pulse is less apt to persist in rheumatic hearts than in old arteriosclerotic hearts because of the difference in the circumstances producing the irregularity. In the first case, it occurs generally when an added strain is put on a decompensated heart, but disappears with improvement in the muscle function. In the second instance, it appears generally as evidence of irreparable damage to the myocardium. In view of these and many similar observations, it is evident that theoretic deductions in connection with the effects of digitalis, in various disorders of the cardiac mechanism or in conditions leading to such disorders, are neither justified nor safe. Each condition requires separate investigation.

⁶ Edens and Huber Ueber Digitalis Bigeminie, *Deutsch Arch f klin Med* **118** 476, 1916.

⁷ Christian, N A The Use of Digitalis in Various Forms of Cardiac Arrhythmia, *Boston M & S J* **173** 306 (Aug 26) 1915.

⁸ Windle, J D Clinical Observations on the Effect of Digitalis in Heart Disease with Pulsus Alternans, *Quart J Med* **10** 275 (July) 1917.

The alarming symptoms of circulatory failure, often supervening rapidly in patients surviving the immediate effects of coronary obstruction, demand heroic treatment. But especial caution is enjoyed in the administration of digitalis in this condition. Various investigators have shown that the occlusion of coronary vessels in animals gives rise to fibrillation of the ventricles.⁹ Digitalis in fatal doses causes ventricular fibrillation almost invariably in the cat, and Reid¹⁰ has reported a similar disturbance with overdigitalization in man. Robinson and Bredeck¹¹ described a patient of whom the electrocardiogram showed a high degree of intraventricular block preceding an attack of ventricular fibrillation. The administration of 1 mg of strophanthin, intravenously, caused an increase in the irregular ventricular complexes simulating the condition of "potential fibrillation" of Levy and Lewis¹² (Necropsy, in this patient, did not reveal any gross interference with the coronary circulation). Since the occlusion of coronary vessels and digitalis may each give rise to fibrillation of the ventricles, and since a potential fibrillary state may obtain which can be exaggerated by digitalis, the inference is natural that such a state may be produced by coronary obstruction and render digitalis in this condition a dangerous drug. There had been no experimental, and very little clinical, evidence when the present investigation was undertaken which throws any light on this subject.

Experiments were, therefore, performed to show whether obstruction to any particular portion of the coronary circulation alters the susceptibility of the heart to the toxic action of ouabain. If it does not, and if a diminished tolerance to digitalis can be created by ligation, such a state should exist in those animals which survive a degree of interference with the coronary circulation causing spontaneous ventricular fibrillation in a large percentage of them.

METHOD AND EFFECTS OF LIGATION

Over fifty experiments were performed on the cat. This animal is particularly well suited to experimentation with digitalis because of

⁹ Smith, F M. The Ligation of Coronary Arteries with Electrocardiographic Study, *Arch Int Med* **22** 8 (July) 1918. Lewis, T. The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, *Heart* **1** 98, 1909. Miller, J L, and Matthews, S A Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, *Arch Int Med* **3** 477 (June) 1909.

¹⁰ Reid, W D. Ventricular Ectopic Tachycardia Complicating Digitalis, *Arch Int Med* **33** 23 (Jan) 1924.

¹¹ Robinson, G C, and Bredeck, J F. Ventricular Fibrillation in Man with Cardiac Recovery, *Arch Int Med* **20** 725 (Nov) 1917.

¹² Levy, A G, and Lewis, T. Irregularities Resulting from Inhalation of Low Percentages of Chloroform Vapor, and Their Relationship to Ventricular Fibrillation, *Heart* **3** 99, 1911.

its resemblance to man in response to this group of drugs¹³. The thoracic cavity was opened by cutting through four or five cartilages close to the sternum, under ether anesthesia and artificial respiration. The pericardium was incised near the base of the heart, and the necessary coronary vessels dissected free for ligation. The thorax was then closed with interrupted sutures and spontaneous respiration resumed, care being taken to close the wound while the lungs were fully inflated. In some of the experiments, the veins were also included in the ligature, in most of them, the arteries only. Necropsies were performed in all cases to confirm the position of the ligature, and to ascertain any gross pathologic changes in the heart.

Certain observations, made during the course of the work, though not directly concerned with the problem, are of sufficient interest to record. In nearly all experiments, ligation of one of the large branches of the coronaries was followed by dilatation of the heart, most pronounced to the right. The effects on the cardiac rhythm of ligation of any of the large branches mentioned in Table 1 were not uniform. For instance, in one experiment, ligation of the right coronary artery resulted in a very slow rate with a 2:1 block, followed in five minutes by ventricular fibrillation. In another experiment, ligation of the right coronary upset the cardiac mechanism in an entirely different manner, there were extrasystoles and periods of extreme tachycardia, followed in six minutes by fibrillation of the ventricles. In other instances, little or no irregularity was seen after ligation of the right coronary. Similar, inconstant disturbances resulted from ligation of the descending branch of the left coronary and of various combinations of branches of the coronary vessels.

The most constant effects were observed after ligation of the entire left coronary artery at the aorta. There was instant blanching of the left side of the heart, with more or less immobilization of the left ventricle, which progressed until the left ventricle practically ceased beating. At the same time, there was dilatation of the right side of the heart, which became livid and continued to beat rapidly and strongly, passing gradually into ventricular fibrillation.

The fibrillation often failed to involve both ventricles. In some instances, it was limited to the right ventricle from the beginning, no movement being perceptible in the left side of the heart, except along the interventricular groove and in a small area at the apex. In other instances, both ventricles fibrillated for the first minute or two, after which the left ceased to show any movement while the right continued to fibrillate. However, both sides of the heart again fibrillated after the ligature was removed and the heart massaged to introduce blood into

¹³ Gold, Harry. Digitalis Elimination, Arch Int Med 32:779 (Nov) 1923

the coronary vessels. In another experiment, ligation of the left coronary produced fibrillation of the right ventricle interrupted by periods of regular beats. Considerable massage and compression of the heart failed to abolish these interruptions. With the removal of the ligature and slight massage to force blood into the coronary artery, both ventricles promptly went into fibrillation which persisted until death, nine minutes later.

The absence of fibrillation in that part of the heart deprived of blood was also observed in experiments in which the descending branch of the left coronary alone was ligated.

The occurrence of the foregoing phenomena in some experiments and not in others, also the variability of the effects, are probably dependent, partly at least, on differences in the compensatory circulation. Several observers have recorded partial fibrillation of the heart. Garrey¹⁴ produced partial fibrillation of the ventricles by electrical stimulation under certain conditions. Lewis¹⁵ also noted in dogs that

TABLE 1.—Incidence of Spontaneous Ventricular Fibrillation Following Varying Degrees of Interference with the Coronary Circulation

Vessels Ligated	Total No of Experi- ments	Ventricular Fibrillation			Time
		Number	Per Cent	31 2	
Descending branch left coronary	16	5	31 2	4 min - 6½ hrs	
Descending branch left coronary and circumflex posteriorly	2	0			
Circumflex branch left coronary	2	0			
Right coronary	7	2	28 5	5 min - 6 min	
Right coronary and circumflex branch left coronary	1	1	33 min		
Descending branch left coronary and right coronary	18	10	55 5	1 min - 2 hrs	
Left coronary	12	12	100 0	1 min - 10 min	

the damaged muscle, resulting from occlusion of a coronary vessel, failed to participate in the fibrillation. In accordance with the theory of circus movement, it is possible that ligating a large branch of a coronary vessel produces a considerable area of impaired conduction so as to confine the circus movement to the remaining portion of the heart. Since the capacity for maintaining fibrillation varies directly as the tissue mass,¹⁴ it is readily seen that the tendency for fibrillation to persist in that portion of the heart not deprived of circulation will vary in different experiments depending on the degree of anastomosis between the coronary vessels. As blood is introduced into the coronary vessel by the removal of the ligature and compression of the heart, the large area of block is abolished and the portion of the heart previously excluded begins to participate in the fibrillation. The larger tissue mass now involved, in turn, makes it more possible for the fibrillation to persist.

14 Garrey, W. E. The Nature of Fibrillary Contraction of the Heart, Its Relation to Tissue Mass and Form, Am J Physiol 33 397 1914

15 Lewis (Footnote 9, second reference)

COMMENT

Table 1 shows the incidence of ventricular fibrillation following varying degrees of interference with the coronary circulation. A large number of animals died during the night of the first or the second day. Since the mode of death was not observed and since factors of infection and shock enter to a greater degree on the second and third days, no deductions are drawn from them except to reckon them among the animals failing to show ventricular fibrillation on the day of ligation. In two experiments, the animals were seen in convulsions, probably from ventricular fibrillation, on the day following the ligations. One of these, in which the descending branch of the left coronary artery was occluded, died immediately after the convulsion, the other, in which the descending branch of the left coronary and the right coronary arteries were ligated, recovered and was injected with ouabain. The percentage of animals showing ventricular fibrillation as a result of coronary ligation given in Table 1 is therefore probably too low, representing only those in which ventricular fibrillation or the convulsion was actually observed.

Of the sixteen experiments in which the descending branch of the left coronary was ligated, five animals, or 31.2 per cent, showed ventricular fibrillation in from four minutes to six and three-fourths hours. In one case, as mentioned above, a convulsion occurred on the second day.

Both animals, in which the descending branch of the left coronary, in addition to the first large descending branch on the posterior surface of the left ventricle, were ligated, recovered without any visible disturbance.

Ligation of the circumflex branch of the left coronary, in two experiments, resulted in no perceptible change in the heart action. Both animals were injected with ouabain on the following day.

The right coronary artery was occluded in seven experiments at one-half centimeter from the aorta. The heart in two animals, or 28.5 per cent, went into ventricular fibrillation in five and six minutes, respectively, after the ligation.

In one experiment, the right coronary and the circumflex branch of the left coronary were ligated, with resulting ventricular fibrillation, in thirty-eight minutes.

Eighteen experiments were performed, in which the right coronary and the descending branch of the left were ligated at the same time. Ventricular fibrillation followed in ten animals, or 55.5 per cent, in from one minute to two hours after ligation.

Tying off the entire left coronary artery at the aorta resulted invariably in ventricular fibrillation in twelve experiments.

Some of the animals in which coronary occlusion was not followed by spontaneous ventricular fibrillation were tested for their tolerance to ouabain. A solution of ouabain, 1:100,000, freshly prepared, was injected slowly into the femoral vein until death occurred. The results are given in Table 2, expressed as the percentage of the average fatal dose of ouabain for the normal cat, taken as 0.1 mg per kilogram of body weight. The average fatal dose of ouabain for the seventeen experiments is 102.3 per cent of the average for normal animals.

In Experiment 11, the animal had a convulsion, presumably from ventricular fibrillation about twenty-two hours after ligation of the descending branch of the left coronary and the right coronary. An

TABLE 2.—Tolerance to Ouabain of Those Animals in Which Coronary Ligation Was Not Followed by Spontaneous Ventricular Fibrillation*

	Vessel Ligated	Time Elapsed Between Ligation and Injection	Fatal Dose of Ouabain After Operation in Percentage of Average Fatal Dose for Normal Animals
1	Descending branch left coronary	1 day	80
2	Descending branch left coronary	1 day	98
3	Descending branch left coronary	1 day	175
4	Descending branch left coronary	1 day	87.2
5	Descending branch left coronary	8 hours	88
6	Descending branch left coronary and circumflex posteriorly	4 hours	141
7	Circumflex branch left coronary	1 day	100
8	Circumflex branch left coronary	1 day	97.1
9	Right coronary	1 day	130
10	Right coronary	1 hour	86
11	Descending branch left coronary and right coronary	1 day	64
12	Descending branch left coronary and right coronary	1 day	103
13	Descending branch left coronary and right coronary	1 hour	104
14	Descending branch left coronary and right coronary	4 hours	105
15	Left coronary	10 minutes	110
16	Left coronary	4 minutes	83.3
17	Left coronary	4 minutes	87.1
Average			102.3

* Two experiments are omitted from the table, the animals having died atypically after ouabain injection.

hour and fifty-five minutes after the convulsion, ouabain injection was started, the heart going into ventricular fibrillation when 64 per cent of the average fatal dose had been injected. This result is an exception to that of the other sixteen experiments. The animal may have been somewhat susceptible to ouabain at the start. An extreme variation above or below the average is occasionally encountered in digitalis testing by the cat method (Experiment 3). In nine instances, in which the ligatures were removed following the production of ventricular fibrillation, the heart recovered a normal beat. But this recovery was only temporary, the heart going back into ventricular fibrillation from thirteen to sixty-eight minutes after recovery. Since, therefore, there is a strong tendency for a recurrence of the ventricular fibrillation even after the ligature is removed, such a recurrence might account for the

small dose of ouabain in the foregoing animal, in which there was recovery following the convulsion and the ligature was not removed

There still remained, however, the consideration that a narrow margin might obtain preceding ventricular fibrillation produced by coronary occlusion, in which fibrillation could be precipitated by digitalis. The foregoing animal, in which the occlusion of the coronary produced a convulsion with spontaneous recovery, might conceivably have been in such a state and, hence, required less ouabain to cause death. It was desirable, therefore, to test this possibility.

Reference has already been made to the occurrence of ventricular fibrillation interrupted by periods of regular heart beats in a number of the experiments. But in none were the intermissions sufficiently long to permit of testing the tolerance to ouabain. Reference has also been made to the nine experiments, in all of which recovery of the normal beat after removal of the ligature was followed in varying periods of time by a recurrence of the ventricular fibrillation. The intermissions, in most of the latter experiments, were, however, sufficiently long to permit of the ouabain injection. The left coronary artery was, therefore, ligated at the aorta in three experiments, with resulting ventricular fibrillation in from four to ten minutes. The ligature was then removed, and the heart, after some massage and compression, resumed a regular beat. Ouabain was then injected as in the previous experiments. The results are shown in Experiments 15, 16 and 17 in Table 2, the animals requiring respectively 110, 83.3 and 87.1 per cent of the normal average fatal dose to cause death. In Experiment 17, after the ligature was removed and the normal beat resumed, a ligature was tied on the right coronary prior to the ouabain injection to add further to any predisposition to ventricular fibrillation which might have already existed. Experiment 13 presented a condition similar to that of Experiment 11 discussed above. The animal had a convulsion, presumably from ventricular fibrillation, one hour and thirty-five minutes after ligatures were tied on the descending branch of the left coronary and the right coronary. Twenty-four minutes after recovery, ouabain was injected, taking thirty minutes for the injection. This animal required 104 per cent of the average fatal dose for the normal animal to cause death.

That the heart in which large branches of the coronary vessels have been occluded is particularly susceptible to some influences causing ventricular fibrillation appears not only from the fact that many go spontaneously into fibrillation but also from the fact that a slight massage, which is without effect on the normal heart, may readily precipitate fibrillation after the ligature has been applied. Nevertheless, the results of seventeen experiments in Table 2 show that the average

fatal dose of ouabain for the group of animals in which various degrees of interference with the coronary circulation prevailed is practically the same as that for normal animals, that the tolerance to ouabain is not affected by ligation of any particular branch of the coronary vessels nor by even extreme degrees of interference. In the light of the data presented, the conclusion is also inevitable that the heart, which as a result of coronary ligation has gone into ventricular fibrillation with spontaneous recovery and which is almost certain again to lapse into ventricular fibrillation, is not necessarily less tolerant to the toxic action of ouabain than the normal heart.

The general tenor of the objections to the use of digitalis in coronary obstruction in man was expressed by Riesman,¹⁶ who said that when the advisability of giving digitalis came up, in a case of coronary thrombosis, he decided not to give it because, in view of the great damage to the myocardium, "it would not do good and might do harm." Theoretically, one could argue both ways. Various degrees of ventricular immobilization take place depending on the degree of impairment of the coronary circulation. This may be partly a protective mechanism against exhaustion. To increase the force of the heart beat in a state of coronary circulation insufficient for greater work might compromise the chance for recovery. On the other hand, one might say that stimulation might help to tide the heart over a period until sufficient collateral circulation is set up to support it. The latter impression was gained by Miller and Matthews in their animal experiments.¹⁷ They also referred to the fact that German writers recommend digitalis in angina pectoris rather than the nitrates.

Herrick¹⁸ stated that the prejudice against the use of digitalis when the myocardium was weak was only partially grounded in fact. He stressed the great value of this drug in coronary occlusion and suggested that quick results be sought in some cases by intravenous or intramuscular injections. Whether digitalis is of any value in the circulatory failure attending coronary obstruction is, however, not within the scope of this investigation. But to conclude from these experiments that digitalis is entirely without danger in coronary occlusion, in man, is hardly justified without further clinical studies. That a functional state of the myocardium may exist in a diseased heart which calls for particular caution in the administration of digitalis, as shown by Robinson and Bredeck, has already been mentioned. A coronary artery may indeed become occluded in a diseased heart which

16 Riesman, D. Coronary Thrombosis, *M. Clin N. A.* **6** 851 (Jan.) 1923

17 Miller and Matthews (Footnote 9, third reference)

18 Herrick, J. B. Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* **69** 2015 (Dec 7) 1912

is already the seat of a high degree of intraventricular block, seen by them in the electrocardiogram. I have simply called attention to the fact that it was mainly from indirect experimental evidence that the inference was drawn that, in man, digitalis might precipitate ventricular fibrillation more readily in the presence of coronary obstruction than in the normal heart. The direct experimental data set forth in this paper lend no support to this belief.

SUMMARY AND CONCLUSIONS

1 More than fifty experiments have been performed on the cat to determine whether coronary occlusion changes the tolerance of an animal to the toxic action of the digitalis bodies.

2 Evidence is cited which shows that theoretic generalizations in connection with the response to digitalis in disturbances of the cardiac mechanism, or in conditions leading to such disturbances, are not justified.

3 Effects of occlusion of different parts of the coronary circulation vary widely, depending on the differences in the compensatory circulation. No constantly occurring irregularities were observed after ligation of any particular branch of the coronary vessels.

4 The failure of the portion of the heart deprived of blood to fibrillate is probably due to an area of block confining the circus movement to the remaining portion of the heart. The failure of the fibrillation to persist after ligation of a large coronary vessel is probably due to the diminished tissue mass involved in the fibrillation.

5 A heart that has been in ventricular fibrillation from coronary occlusion and has recovered temporarily also shows no diminished tolerance to the toxic action of digitalis (ouabain).

6 The average fatal dose of digitalis (ouabain) for seventeen animals with varying degrees of coronary obstruction was the same as that for normal animals. The experimental data, therefore, lend no support to the fear that in the presence of coronary occlusion digitalis may precipitate ventricular fibrillation more readily than in the normal heart.

THE EXPERIMENTAL PRODUCTION OF HYPERTENSION

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Hypertension, chronic nephritis and their related heart conditions are subjects of increasing interest because they are causing more deaths than any other disease process. This may be due, in part, to the prolongation of life. A larger number of persons are thus allowed to enter the decade of life when degenerative cardiovascular and renal conditions are most prone to occur. If the span of life is further increased, as seems likely, degenerative lesions will affect a still larger number of persons.

In spite of the great amount of work that has been done, the cause of high blood pressure and its frequently associated chronic nephritis has not been determined. The clinical importance of this subject warrants continued search for the causes of these conditions.

The rôle of excessive protein metabolism as an etiologic factor in arteriosclerosis and chronic nephritis has long been a matter of debate. There are many students of this question who feel that excessive protein diets are directly responsible for the degenerative vascular-renal diseases. There are others who are equally positive that this theory is wrong. One of the contentions raised against this relationship is that an increase in blood pressure has not been produced experimentally by feeding diets high in protein.

In this preliminary report, we wish to record some of the results of a carefully conducted group of experiments in which the relationship between high protein diets and blood pressure was studied. In three groups of rabbits on high protein diets for twenty-one months, which is the duration of the experiments to date, an increased blood pressure has developed and persisted. In a fourth group of control animals, kept under the same conditions as the others, the diet alone differing, the blood pressure has continued at a normal reading for a rabbit, which is from 70 to 80 mm of mercury.

The difficulty in obtaining satisfactory blood pressure readings, in experimental animals over long periods of time, is responsible for the small amount of work done along these lines. We have succeeded in

* From the laboratories of the Potter Memorial Clinic and the Santa Barbara Cottage Hospital

finding only one reported group of experiments in which the blood pressure was followed for a definite period of time. Schmidtmann¹ took blood pressure readings for periods varying from five to nine months. Using a slight modification of the method suggested by von Eweyk and

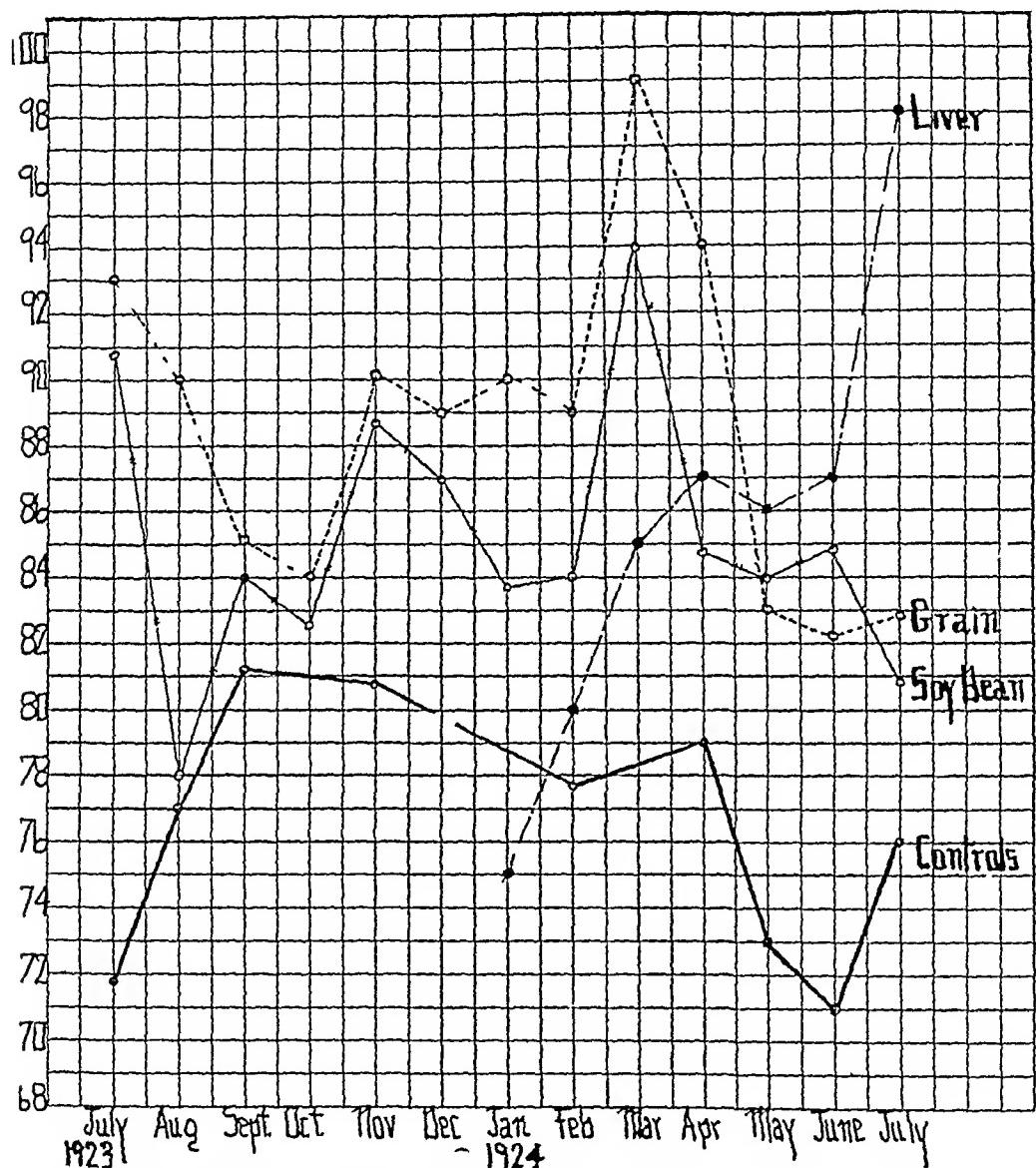


Chart 1—Average range of blood pressure for one year in control and high protein diet groups of animals

Schmidtmann,² we have taken the blood pressure of our animals one or more times a month for the last twenty-one months.

Two persons are necessary in making these determinations. The rabbit, with a bandage over its eyes, is held in the lap of an assistant

1 Schmidtmann, M. Experimentelle Studien zur Pathogenese der Arteriosklerose, Virchows Arch f path Anat 237:1, 1922.

2 Van Eweyk, C., and Schmidtmann, M. Zur Methodik der Blutdruckmessung beim Kaninchen, Virchows Arch f path Anat 236:420, 1921.

In this position, it seldom struggles. The blood is compressed from the foreleg by winding a rubber bandage from the toes upward. A small rubber cuff is then placed about the upper part of the leg. The cuff is connected with a mercury manometer (Baumanometer) and inflated to from 140 to 150 mm of mercury. The compressing bandage is then removed from the lower part of the limb. A pea sized piece of skin is snipped off the front of the leg over the anterior tibial artery. The pressure in the manometer is allowed to drop until the blood is seen to shoot down through the artery, which is exposed through the window in the skin. A second check on this reading is obtained by observing the pressure at which the small capillaries in the skin at the edges of the window begin to ooze. This occurs at about 20 mm of mercury lower pressure than the reading obtained by noting the sudden filling of the larger artery. Repeated readings may be made through the same window during an afternoon. Following the final reading, the window is painted with iodin, and the animal replaced in its cage. The wound is entirely healed within from seven to ten days. We have had no instances of infection following several thousand blood pressure determinations.

The results of the average of the monthly readings of twelve normal (control) rabbits from July, 1923, to July, 1924, is recorded in Chart 1. It will be noted that the average pressure varied between 72 and 81 mm of mercury.

A second group of twelve rabbits, whose phenolsulphonephthalein output ranged from 65 to 80 per cent, whose urines contained neither albumin nor casts, whose blood nonprotein nitrogen, urea nitrogen and carbon dioxid were within normal limits, and whose systolic blood pressure ranged between 72 and 78 mm of mercury over a period of three months, was placed on a diet high in liver protein.

The criticism that has been raised about work done by Newburg and Clarkson³ and others concerning the production of arteriosclerosis and kidney damage, in feeding experiments, has been that our present knowledge of foods does not permit us to make deductions concerning one factor as protein when other food components are deficient in amount or quality. To avoid this criticism, we used, for this group of animals, a diet originally suggested by McCollum,⁴ which contains all the elements essential to growth and maintenance. It consists of liver, 20 per cent, casein, 20 per cent, maize, 20 per cent, wheat, 30 per cent, navy beans, 5.5 per cent, cod liver oil, 2 per cent, calcium carbonate, 1.5 per cent, and salt, 1 per cent. Six weeks following the

³ Newberg, L. H., and Clarkson, Sarah. Renal Injury Produced in Rabbits by Diets Containing Meat, *Arch Int Med* **22** 850 (Dec) 1923.

⁴ Polvogt, L. M., McCollum, E. V., and Simmonds, Nina. The Production of Kidney Lesions in Rats by Diets Defective Only in That They Contain Excessive Amounts of Protein, *Bull Johns Hopkins Hosp* **34** 168 (May) 1923.

starting of this diet, the blood pressures of these animals were elevated without exception. This increase in pressure has continued, as is shown in Chart 1. The nonprotein nitrogen and the urea nitrogen of the blood increased in amount, and the urine regularly contained casts and albumin after the sixth week of the experiment (Charts 2 and 3). The reaction of the urines in this group has been acid.

A third group of twelve rabbits, after having been studied so as to exclude any that might have a spontaneous nephritis, was placed on a

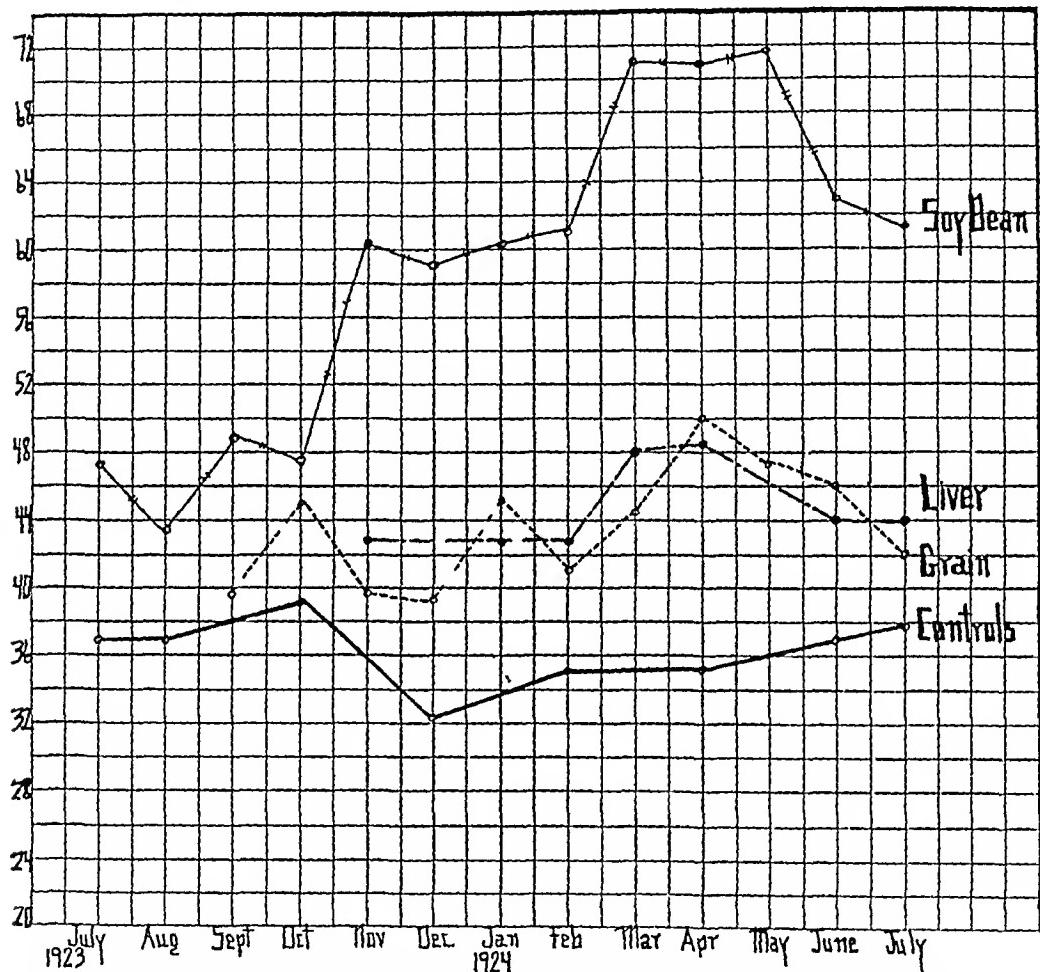


Chart 2.—Range of nonprotein nitrogen per hundred cubic centimeters of blood for period of one year in four groups of animals.

16 per cent oat protein diet. The bulk of this diet consisted of oats, but cod liver oil and tomato were given ad libitum, and alfalfa was given at intervals to prevent the development of deficiency diseases from lack of vitamins. Six months after this diet was started, the blood pressures were elevated and have continued elevated to the present (twenty-one months). The urine contained albumin and casts by the fourth and the fifth month. The nonprotein nitrogen and urea nitrogen of the blood has increased in amount (Charts 2 and 3). The reaction of the urine is acid.

A fourth group of twelve normal rabbits was placed on a 38 per cent soy bean protein diet. In addition to the soy beans, cod liver oil, tomato and alfalfa were given, as stated above. Within four months, an elevation of the blood pressure was noted. Albumin was not found regularly in the urine until almost a year after the protein feeding was commenced. An increase in the nonprotein nitrogen and urea nitrogen of the blood was noted in the ninth month. This, too, has continued. The urine of this group has remained alkaline.

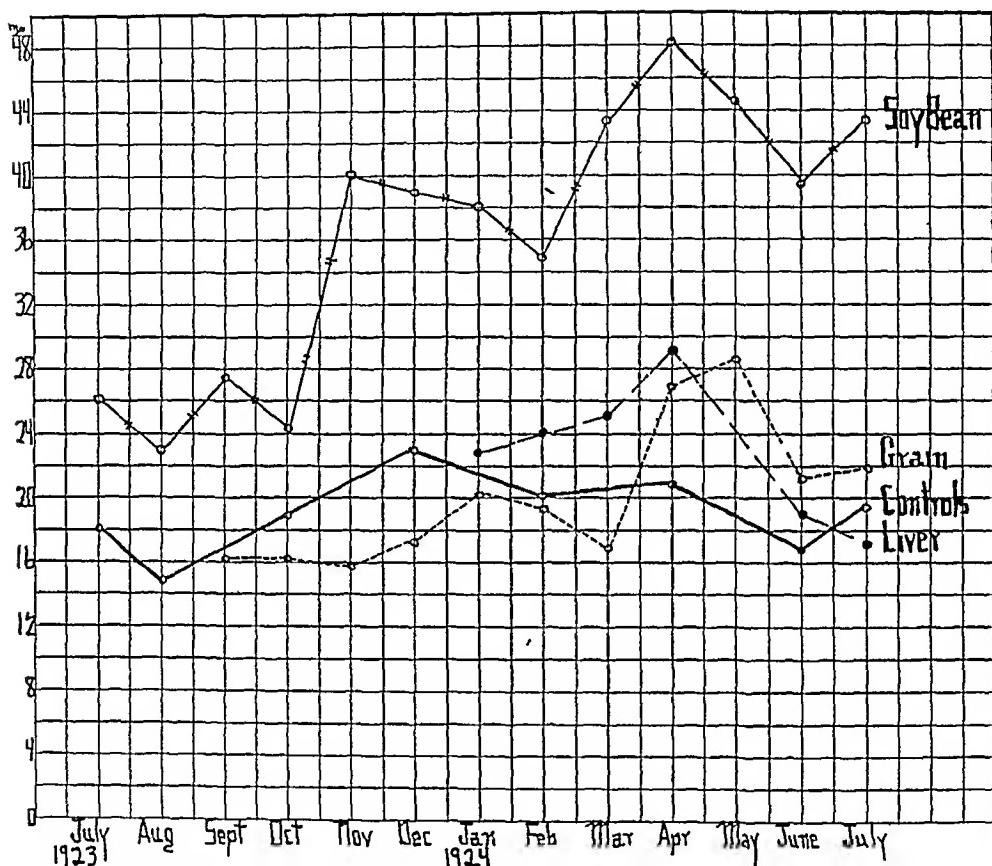


Chart 3.—Range of urea nitrogen per hundred cubic centimeters of blood for period of one year in four groups of animals.

On the completion of these experiments, a careful pathologic study will be made of the kidneys, blood vessels, liver and other viscera. It would seem that marked changes would be found.

COMMENT

The results of our experiments suggest that excessive protein diets will cause an increase in blood pressure. In addition, evidence of disturbed renal function is found by the presence of albumin and casts in the urine, and by the increase of nitrogenous end products, nonprotein nitrogen and urea nitrogen in the blood.

The increase in blood pressure has been most marked in the group of animals on a liver protein diet. The presence of albumin and casts in the urine and the increase in pressure were noted at the sixth week of the experiment, which is earlier than such changes occurred in the other groups. The blood pressures in the group fed on soy bean protein were elevated before changes occurred in the urine or in the blood.

The possibility that acid ash diets necessitating the excretion of highly acid urines over long periods of time might be responsible for the development of high blood pressure and degenerative kidney lesions

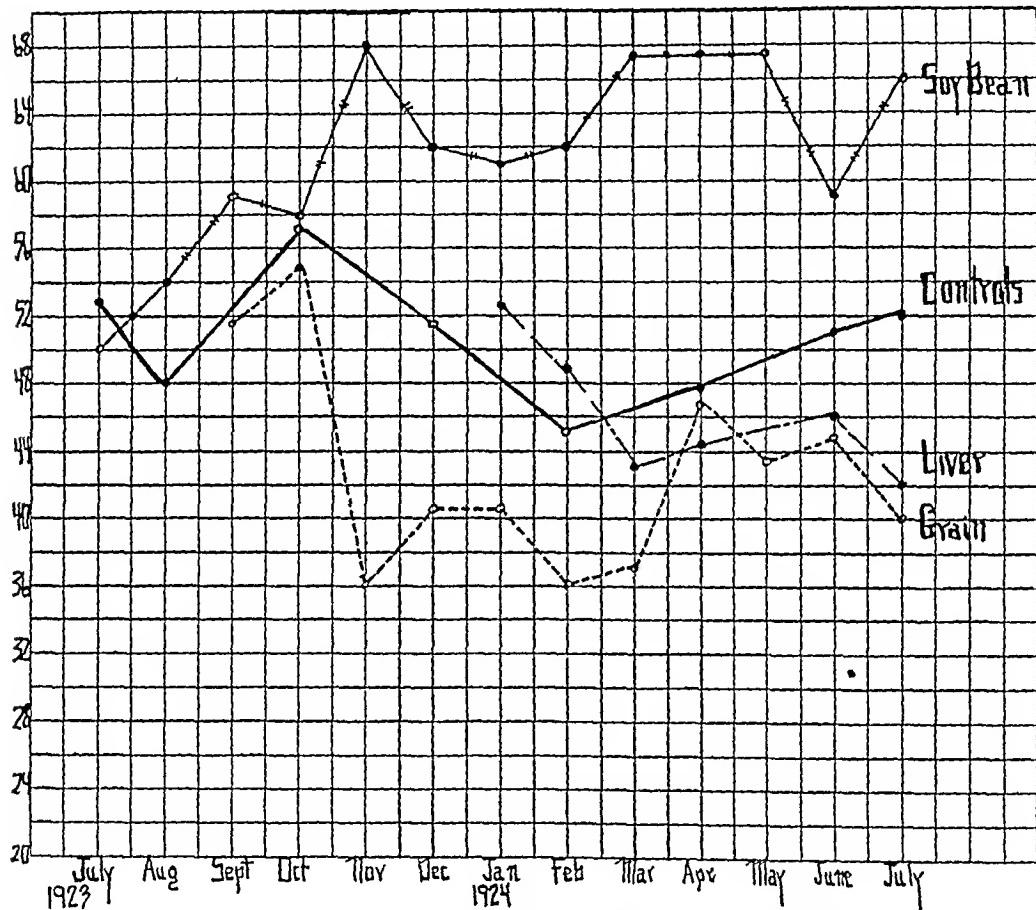


Chart 4.—Range of carbon dioxide capacity of blood plasma for one year in four groups of animals, per cent by volume.

is a new suggestion. Clinically, there are facts that give weight to this theory. Among these is the unmistakable improvement that occurs in persons with hypertension and chronic nephritis when placed on a basic (alkaline) diet. The oat group of experimental animals have continuously acid urines, due to the acid ash of the oat protein. The soy bean group have shown an elevation of the blood pressure and changes in the blood and urine while the alkaline ash of the soy bean has kept the urines alkaline. The carbon dioxide of the blood serum has remained high in this group, whereas, in the liver and oat protein groups, these

readings have been lower than in the control group. The occurrence of these changes, in the group whose urines are alkaline, does not invalidate the foregoing theory regarding the causation of hypertension and chronic nephritis.

Fisher⁵ produced nephritis by the exhibition of excessive alkali. The soy bean diet gives a very alkaline reaction to the urine. The hydrogen ion concentration of these urines ranges from 8.8 to 9. A

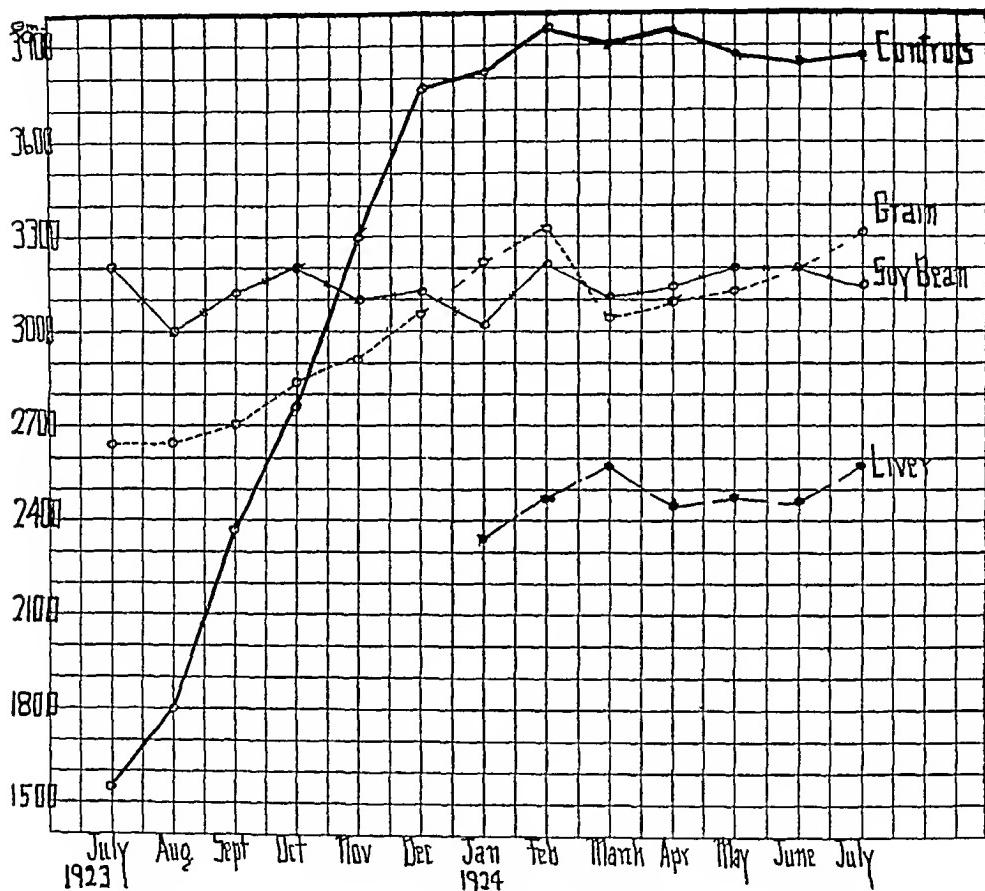


Chart 5.—Increase in weight from July, 1923, to July, 1924.

neutral urine has a p_H of 7. The excessively alkaline ash diet, as evidenced by the excretion of an abnormally alkaline urine for many months, might well be responsible for the changes that we have noted.

The weight curves (Chart 5) indicate a graduate increase in all groups of animals. The controls are now the largest animals. The soy bean group still appear in good condition. The fur of the oat and liver groups has become dry, and these animals are not so robust.

5 Fisher, Martin. Edema and Nephritis. New York, John Wiley & Sons, p. 428.

We are giving special attention to particular metabolites of the non-protein nitrogen group to see if an increase of the amino acids or of guanidin is present Major⁶ has recently called attention to the pressor effect of guanidin bases

SUMMARY

Three groups of rabbits placed on high protein diets, each group on a different type of protein, developed an increased blood pressure

Evidence of renal irritation was offered by the appearance and persistence of albumin and casts in the urines of these animals, and by a retention of nonprotein nitrogen and urea nitrogen in the blood There also was evidence of acidosis, as shown by a continued decrease in the carbon dioxide of the blood plasma of the oat and liver protein groups of animals This decrease in the carbon dioxide was not present in the soy bean group, whose urines were alkaline

It is suggested that diets containing an excessive acid or alkaline ash, necessitating the excretion of excessively acid or alkaline urines over long periods of time, might, in themselves, be responsible for degenerative blood vessel and kidney changes

⁶ Major, R. H. Relationship Between Certain Products of Metabolism and Hypertension, J. A. M. A. 83: 81 (July 12) 1924

THE EFFECT OF INGESTION OF YEAST ON THE LEUKOCYTE COUNT*

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When a foreign protein is injected into the blood stream, it has been observed that the number of leukocytes is at first usually diminished, later markedly increased and that finally there is a gradual decrease, the number of leukocytes falling to approximately the original level. It also has been observed that during the height of digestion and absorption in the small intestine, the leukocytes are increased in number.

In connection with a study on the effect of ingestion of yeast in certain pathologic conditions, we were interested in a consideration of the mechanism of its action. In cases of infection, it is generally assumed that an increase in the number of leukocytes indicates a satisfactory response on the part of the organism in defending itself against the invading bacteria. There are, however, numerous investigators who do not believe that an increase in the leukocyte count necessarily accompanies such a defensive response. It has been observed that no improvement occurred with marked leukocytosis, and that marked improvement may occur without leukocytosis.

The ingestion of yeast has been assumed to produce a leukocytosis. Failing to find any literature on this subject, we undertook experiments to study the effect of the ingestion of yeast on the leukocyte count.

EXPERIMENTS

For the purpose of such experiments, we appealed for volunteers to the members of the present first and second year classes in the University of Illinois College of Medicine. Twenty-two members of these two classes volunteered and thus made this work possible. The method of procedure was as follows:

The blood samples were taken at 9:30 a.m. on eight successive mornings. All these subjects were requested to attempt to maintain a reasonable uniformity in their diets and physical activities. The morning meal was supposed to have been ingested at approximately the same period of time before the taking of the blood sample. The leukocyte count was made as follows:

A standard white pipet and Thoma-Zeiss hemocytometer were used in this work. The first drop of blood was wiped away and the second

* From the University Hospital and the Laboratory of Physiological Chemistry, University of Illinois College of Medicine.

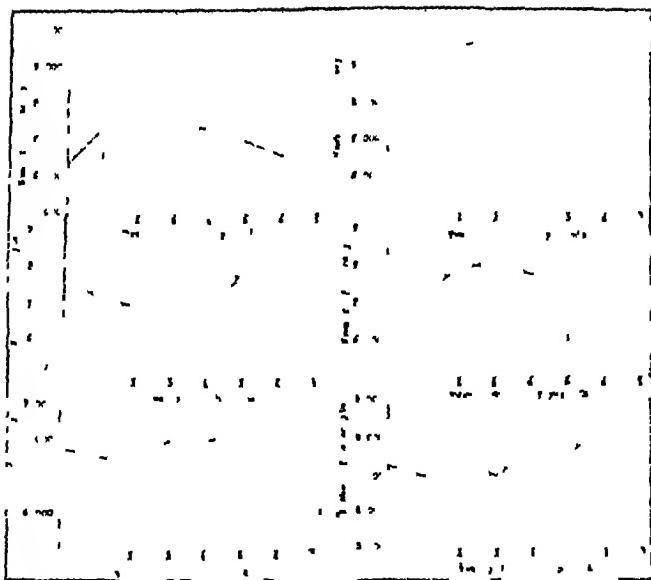


Chart 1—Curves showing normal variations

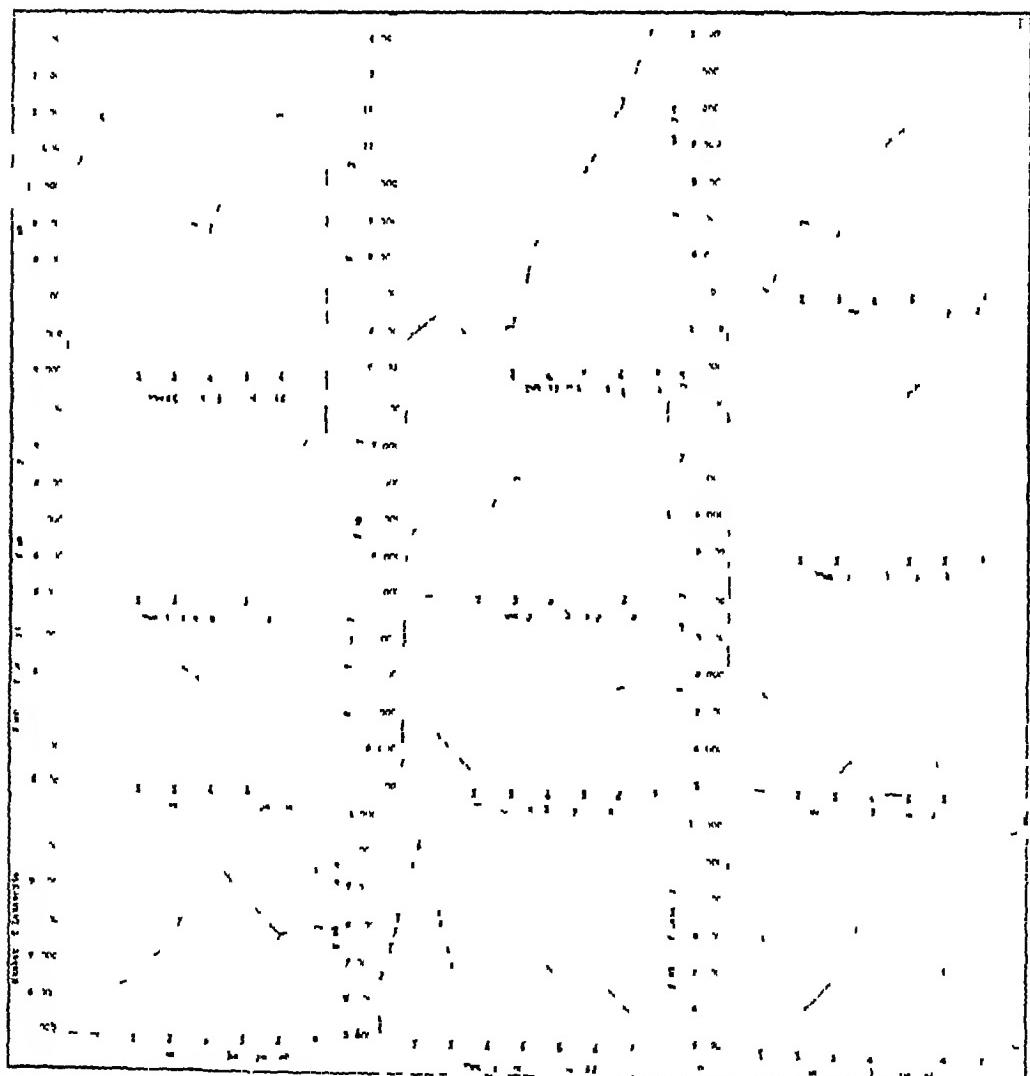


Chart 2—Curves showing effect of ingestion of yeast on leukocyte count

drop drawn to the 0.5 mark. The blood was diluted one-twentieth with 1 per cent acetic acid, and the average count of 5 large squares (1 sq mm) taken. This was multiplied by 200 to give the normal count in one cubic millimeter.

Six of the ten subjects that we studied with a view to establishing a base line showed a small amount of variation from day to day. Three of the remaining four developed mild respiratory infections. At the time the symptoms became noticeable, there was a marked increase in the leukocyte count. The tenth subject showed a decided rise in the leukocyte count, during the latter part of the period, without our being able to arrive at any explanation. The six curves (Chart 1) furnish a base line for comparison with the curves obtained from the subjects who were given yeast. The maximum variation obtained in these six curves is 1,600.

The subjects who aided us in the study of the effect of yeast reported, the first day, without any yeast ingestion, after the blood count was taken, they ingested three cakes of one of the common market varieties of fresh yeast (Fleischmann) per day—one cake between breakfast and lunch, one cake between lunch and dinner, and one cake between dinner and the time of retiring. This was continued for seven days. The subjects were carefully watched for infections or other conditions which might alter the count. No such infections or conditions were observed. Our results are shown in Chart 2. In some cases there is no initial diminution in the leukocyte count. Possibly, the interval of twenty-four hours between the first and the second counts was sufficiently long so that the decrease had disappeared and increase had begun. Some of the cases did not show a marked increase in the number of leukocytes. However, the majority of these cases studied showed a definite increase in the leukocyte count, which was much greater than the normal variation under the conditions of our experiment.

We are indebted to Drs. Brooke and Lorfeld for the technical assistance in this work.

SUMMARY

On the basis of these results we conclude that in most cases the ingestion of three cakes of yeast daily causes a marked increase in the leukocyte count in apparently normal persons.

MERCUROCHROME-220 SOLUBLE AS A BILIARY ANTISEPTIC

AN EXPERIMENTAL STUDY *

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AND

W W SCOTT, M.D.

BALTIMORE

Although there have been many experimental and clinical attempts to find a biliary antiseptic,¹ so far no drug has been shown to have a sufficiently strong or constant therapeutic action in bile to afford a solution of this important problem. Surgical intervention, which hitherto has been the most satisfactory method of treatment, theoretically is not the method of choice. Aside from its own difficulties, it often fails to eliminate the infection, especially in cases in which the bile passages and liver are involved.² Moreover, even in cases of cholelithiasis requiring surgical treatment, it would be of great value to control an accompanying infection before operation. If, therefore, a drug can be found which can be shown to be excreted by the liver, to be present in the bile in bacteriostatic or bactericidal strength, and to be of low enough toxicity to allow its safe clinical use, it would be of great value in the treatment of biliary infections. The use of such a drug would be indicated not only in the treatment of active infections, in which both the alleviation of the immediate condition and the relation between infection and cholelithiasis³ are important, but also in the treatment of infections of the latent or chronic type, especially as found in bacterial carriers.

A variety of organisms must be considered in the study of biliary antisepsis. Of these, *Enterobacter typhi* (*B. typhosus*) has been the most thoroughly studied.⁴ *Salmonella paratyphi* (*B. paratyphosus A*), *Salmonella schottmulleri* (*B. paratyphosus B*), the colon group bacilli, *Enterobacter paradysenteriae* (*Hiss*) and (*Flechner*) and *vibrio comma*, and the staphylococci⁵ should be considered.

A resumé of the numerous previous attempts to find a biliary antiseptic of value against one or more of these organisms shows the lack of success in this search so far, and indicates clearly the value of studying mercurochrome-220 soluble from this point of view. This study is also suggested because, since the original presentation of mercurochrome-220 as a local germicide,⁶ the possibility of its use intravenously and also of its administration by mouth has been shown.⁸ Working simultaneously

* From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital

with us, Rosenthal and White⁹ have shown that mercurochrome is eliminated through the bile. They say

Mercurochrome departs from the blood more rapidly than flumerin, and is excreted in the bile in larger quantities. Thus in two rabbits there was an average biliary excretion of 25 per cent in one hour and 44 per cent in the two hours after injection.

Our own experiments on the excretion of mercurochrome in bile are shown in Tables 1 and 2. The method employed consisted of ligating the common duct of a rabbit, under ether anesthesia, and inserting a drainage tube into the fundus of the gallbladder. Through this drainage tube, specimens of bile were collected, a control specimen before drug administration always being obtained. The appearance time of the drug was noted. As the readings of drug concentrations in bile are difficult, after approximate whole bile observations, the bile pigments were dissolved by the addition of an equal part of Schlessinger's solution (10 per cent solution of zinc acetate in alcohol) to each specimen. After allowing the sediment to settle, direct readings could be made against standard mercurochrome dilutions. These tests proved to be of value, for in highly colored bile the presence of the drug was revealed in this way, when otherwise it would have been impossible to detect it.

These tables show that the drug first appears in the bile about fifteen minutes after an intravenous injection of 5 mg per kilogram of body weight, that it is present in its strongest concentration, from 1:5,000 to 1:25,000, the first two hours after injection, that it continues to be excreted in a concentration of from 1:8,000 to 1:50,000 the next two hours, and that it has been entirely eliminated in twenty-four hours. That is, by intravenous administration, mercurochrome reaches the bile quickly, is present in strong concentration for at least four hours, and is gone in twenty-four hours. Giving the drug by stomach, however, results in its appearance in the bile much more slowly—approximately the second hour after administration—and in concentrations weaker than those obtained by intravenous injection but still of bacteriostatic or bactericidal strength, as will be shown later. By properly adjusting the dosage of drug administered by mouth, it should be possible to obtain a constant presence of drug in the bile, which could be continued for at least a week, as Young, Scott and Hill⁸ have shown that 900 mg a day of mercurochrome by mouth may be given clinically for a week or more without injury. In these experiments, therefore, the first requirement for a biliary antiseptic has been met, namely, it has been shown that mercurochrome-220, given intravenously or by mouth, is excreted through the bile in strong concentrations.

In studying the germicidal action of mercurochrome in bile, three methods have been used first, entirely *in vitro* tests in bile, second,

combined in vivo-in vitro tests, in which the germicidal action of bile after the administration of mercurochrome was tested, and third, combined in vivo-in vitro tests, in which the germicidal action of bile after the administration of mercurochrome was tested, and third,

TABLE 1.—*Appearance Time and Approximate Concentration of Mercurochrome-220 in Gallbladder Bile After Intravenous Injection of 5 Mg Per Kilogram to Rabbits*

Time	Rabbit A		Rabbit B	
	Whole Bile Readings	Pigment Free Readings	Whole Bile Readings	Pigment-Free Readings
1 Before injection, control	No drug	0	No drug	0
2 0 to 15 minutes after drug	13 minutes, color change, 14 minutes, definite drug	0	No definite drug	0
3 16 to 30 minutes after drug	Drug increasingly strong, very heavy by 27 minutes		Sixteenth minute, trace, eighteenth minute, drug present, eighteenth to thirtieth minute, increasingly strong	1 6,000
4 31 to 45 minutes after drug	Drug strong throughout	1 5,000	Drug strong throughout	1 5,000
5 46 to 60 minutes after drug	Drug strong throughout	1 5,000	Drug strong	1 5,000
6 1 to 1½ hours after drug	Drug very strong	1 7,000	Drug strong	1 6,000
7 1½ to 1½ hours after drug	Drug very strong	1 7,000	Drug strong	1 6,000
8 1½ to 1½ hours after drug	Drug strong	1 25,000	Drug strong	1 6,000
9 1½ to 2 hours after drug	Drug strong	1 25,000	Drug strong	1 6,000
10 2 to 2½ hours after drug	Drug strong	1 20,000	Drug strong	1 8,000
11 2½ to 2½ hours after drug	Drug strong	1 25,000	Drug strong	1 8,000
12 2½ to 2½ hours after drug	Drug strong	1 30,000	Drug strong but less	1 10,000
13 2½ to 3 hours after drug	Drug strong	1 30,000	Drug strong	1 15,000
14 3 to 3½ hours after drug	Drug present	1 35,000	Drug strong	1 20,000
15 3½ to 3½ hours after drug	Drug present	1 40,000	Drug strong	1 20,000
16 3½ to 3½ hours after drug	Drug present	1 40,000	Drug present	1 30,000
17 3½ to 4 hours after drug	Drug present	1 50,000	Drug present	
18 24 hours after injection (15 minute specimen)	No drug	0	No drug	0

TABLE 2.—*Appearance Time and Approximate Concentration of Mercurochrome-220 in Gallbladder Bile of Rabbits After Mercurochrome-220 by Mouth*

Time	Rabbit A		Rabbit B	
	1 Dose of 50 Mg per Kg	2 Doses of 50 Mg 4 Hrs Apart	Whole Bile Readings	Pigment Free Readings
Before treatment	No drug	0	No drug	0
First hour after dose	Very slight trace, bile dark	1 100,000	No visible drug, bile dark	0
Second hour after dose	Drug present	1 25,000	Drug present	1 25,000
Third hour after dose	Drug present	1 50,000	Drug present	1 50,000
Fourth hour after dose	Drug present	1 50,000	Drug present	1 100,000
Fifth hour after dose	Drug present	1 55,000	Second Dose, 50 mg	
Sixth hour after dose	Drug present		Drug present	1 50,000
Seventh hour after first dose	Drug present		Drug strong	1 25,000
Eighth hour after first dose			Drug strong	1 20,000
24 hours after first dose			Drug present	1 50,000
			No visible drug	1 100,000

entirely in vivo tests, that is, the action of the drug intravenously and by mouth on rabbit gallbladder infections with *Escherichia typhi*. These groups of tests will be discussed separately.

IN VITRO TESTS

In all these, the method of Beckwith¹⁰ was used because it was found to be very satisfactory, and because we desired to have our results as comparable to his as possible. For this reason, through the kindness of Dr Beckwith, a culture of *B. typhosus* 3 was obtained. As the action of mercurochrome in salt solution and serum had been studied previously,¹¹ we limited our tests to ox bile, freshly sterilized by autoclaving for twenty minutes at 15 pounds (6.8 kg.) pressure.

The essentials of the method, the exact details of which may be found in Beckwith's article,¹⁰ are as follows. Small agglutination tubes carefully cleaned and sterilized were used, each tube receiving 0.9 cc. of bile, except the bile control tubes, which received 1 cc. Dilutions were made by adding 0.1 cc. of mercurochrome-220 dilution in bile, ten times the finally desired concentration of drug, to 0.9 cc. of bile. Preliminary tests were done with the dilutions used by Beckwith, that is, 1:1,000, 1:10,000, 1:100,000, and 1:1,000,000, but, as the zones of action were more clearly defined, finally dilutions of 1:1,000, 1:5,000, 1:10,000, 1:25,000, 1:50,000, 1:75,000, 1:100,000 and 1:250,000 were used. In Table 3, in which the results of these tests are given, the killing strength indicates failure to kill at the next dilution in the series just enumerated. Having made and carefully mixed these dilutions of mercurochrome in bile, each tube was inoculated with two loopfuls of a twenty to twenty-four hour broth culture of the test organism, using 0.4 mm. platinum wire with an oese 2 mm. in diameter. Immediately after inoculation, plates were streaked with one loopful of the mixture to control the experiment, and subsequent transfers were made one, two, five and twenty-four hours after inoculation. Parallel series of transfers were also made to broth, as the plate method was found to offer difficulties in certain drug concentrations in which inhibitive amounts of drug were carried over to the agar. In every series the greatest care was taken to inoculate control tubes in drug-free bile with every organism, for the possible bactericidal action of bile has long been noted, especially by Leibuscher,¹² Neufeldt,¹³ Talma,¹⁴ Braun,¹⁵ Fornet,¹⁶ Meyerstein,¹⁷ Pies,¹⁸ Nichols,¹⁹ and Beckwith and Lyon.²⁰ The results of these in vitro tests (Table 3) show that, in bile, mercurochrome in a concentration of 1:1,000 kills all the organisms tested, with the exception of *Staphylococcus aureus*, in one hour, and that in a concentration of 1:5,000 it kills *B. typhosus* 3 in the same length of time. In five hours, with the exception of *Salmonella paratyphi* (*B. paratyphosus A*), *Vibrio comma* and *Staphylococcus aureus*, all organisms were killed in a concentration of 1:25,000, while the twenty-four hour killing strength, excepting *Staphylococcus aureus*, varied from 1:50,000 to 1:100,000. Although too close a comparison cannot be made between different tests,

by comparing these figures with concentrations of mercurochrome found in bile after administration to rabbits, it will be seen that germicidal action in vivo could be expected.

TABLE 3—Action of Mercurochrome-220 in Bile in Vitro

Organism	Drug Concentration Killing in One Hour	Drug Concentration Killing in Two Hours	Drug Concentration Killing in Five Hours	Drug Concentration Killing in Twenty-Four Hours	Drug-Free Bile Control
<i>Eberthella typhi</i> B (Beckwith) (B. typhosus)	1 5,000	1 5,000	1 25,000	1 50,000	Good growth 24 hours
<i>Eberthella typhi</i> (Rawlings)	1 1,000	1 5,000	1 25,000	1 75,000	Good growth 24 hours
<i>Salmonella paratyphi</i> (Paratyphi A)	1 1,000	1 5,000	1 10,000	1 100,000	Good growth 24 hours
<i>Salmonella schotmulleri</i> (Paratyphi B)	1 1,000	1 5,000	1 25,000	1 100,000	Good growth 24 hours
<i>Eberthella paradysenteriae</i> Flexner (B. dysenteriae Flexner)	1 1,000	1 5,000	1 25,000	Bile control bactericidal through 5 repeatedly hour tests	Good growth
<i>Eberthella dysenteriae shiga</i>	1 1,000	1 1,000	1 25,000	Bile control bactericidal through 5 repeatedly hour tests	Good growth 24 hours
<i>Escherichia communior</i> (B. coli)	1 1,000	1 1,000	1 25,000	1 75,000	Good growth 24 hours
<i>Vibrio comma</i>	1 1,000	1 5,000	1 10,000	1 50,000	Good growth 24 hours
<i>Staphylococcus aureus</i>	1 100	1 100	1 1,000	1 5,000	Good growth 24 hours

IN VIVO-IN VITRO TESTS

In vivo-in vitro tests, specimens of bile taken from rabbits before and after the administration of mercurochrome were inoculated with *B. typhosus* and tested as in the entirely in vitro tests, that is, one loopful removed just after inoculation and at intervals thereafter, plated and put in broth.

EXPERIMENT 1—The rabbit had the common duct ligated and the drainage tube inserted in the gallbladder, and, after recovery from the ether anesthesia, was given 5 mg per kilogram of body weight of mercurochrome, intravenously, specimens of bile being taken before drug administration, and for four hours after injection. There was a delay in appearance of the drug in the bile, until forty-five minutes after injection, which was found to be due to the position of the animal.

TABLE 4—Results in Experiment 1

Specimen	Before Inoculation, Bile Sterility	Organisms One Minute after Inoculation	Organisms One Hour after Inoculation	Organisms Twenty Four Hours after Inoculation
	Control	Inoculation	Inoculation	Inoculation
Normal (before drug)	Sterile	Heavy	Heavy	Heavy
First hour after drug (appearance time 45 minutes)	Sterile	Heavy	Heavy	Heavy
Second hour after drug	Sterile	Heavy	Heavy	Sterile
Third hour after drug	Sterile	Heavy	Heavy	Sterile
Fourth hour after drug	Sterile	Heavy	Heavy	Sterile

In this experiment, the bile before drug administration allowing a heavy growth of *Eberthella typhi* twenty-four hours after inoculation, the specimens taken two, three and four hours after drug administration killed the organisms in twenty-four hours.

EXPERIMENT 2—This experiment was done by one of us (J H H) with Rosenthal,⁹ and was prepared first for this paper. A rabbit was given 5 mg per kilogram of body weight of mercurochrome intravenously, and bile specimens were taken before administration and thirty minutes, one hour and two hours after administration, 2 c.c. of each specimen being inoculated with 0.1 c.c. of a twenty-four hour broth culture of *B. typhosus* 3 and transfer made to agar at once after inoculation, and one, sixteen and twenty-four hours after inoculation.

TABLE 5.—Results in Experiment 2

Specimen	Before Inoculation,	Organisms One Minute after Inoculation	Organisms One Hour after Inoculation	Organisms Sixteen Hours after Inoculation	Organisms Twenty Four Hours after Inoculation
	Bile Sterility	Inoculation	Inoculation	Inoculation	Inoculation
Normal 1 (before drug)	Control Three colonies <i>Staphylococcus albus</i>	Heavy <i>Eberthella</i> and one colony <i>Staphylococcus</i>	Heavy <i>Eberthella</i> and two colonies <i>Staphylococcus</i>	Heavy, both or ganisms	Heavy, both or ganisms
Normal 2 (before drug)	Moderate growth <i>Staphylococcus albus</i>	Heavy <i>Eberthella</i> two colonies <i>Staphylococcus</i>	Heavy, both or ganisms	Heavy, both or ganisms	Heavy, both or ganisms
Thirty minutes after drug	Moderate growth <i>Staphylococcus albus</i>	Heavy	Sterile	Sterile	Sterile
One hour after drug	Two colonies <i>Staphylococcus albus</i>	Heavy	Sterile	Sterile	Sterile
Two hours after drug	Three colonies <i>Staphylococcus albus</i>	Heavy, one colony <i>Staphylococcus</i>	Sterile	Sterile	Sterile

In this case, with the control or drug-free specimens allowing a heavy growth of the inoculum, *Eberthella typhi*, and no diminution of the contaminating *Staphylococcus albus* within thirty minutes after drug administration, the bile had become sufficiently bactericidal to kill the large number of organisms inoculated, as well as the staphylococcus, in one hour. Better bactericidal action than this we believe it would be difficult to demonstrate.

IN VIVO TESTS

As Beckwith has shown, especially with the flavines, that drugs active in bile in vitro may not be of use in eliminating biliary infections, we have tested the action of mercurochrome on rabbits with gallbladder infections of *B. typhosus* 3. The infections were obtained by intravenous inoculations, or, more satisfactorily, by direct inoculation of the gallbladder. Even when using the latter method, we felt that it was necessary to control the experiments in two ways, first, by obtaining a positive culture from the bile before treatment and, second, by examining a series of untreated rabbits which had received the same inoculation. The protocols of the experiments are given in Table 6.

From this table, it will be seen that after single intravenous injections of 3 and 5 mg per kilogram of body weight no organisms could be recovered from the bile of animals in which the infection had been

TABLE 6.—Treatment of *S. s.* during Treatment Period

demonstrated previously by culture of the bile. Similarly, no organisms were found after repeated intravenous injections of 5 mg per kilogram of body weight. The bile was found to be sterile after administration of a total of fourteen doses of the drug (two doses daily of 7.5 mg per kilogram) by mouth. The controls, on the contrary, were positive in every case, the gallbladders of these animals also showing macroscopic evidence of persisting infection.

SUMMARY

It has been shown that mercurochrome is excreted by the liver, that it appears in the bile in strong concentrations, that bile after the intravenous administration of the drug is bactericidal when inoculated with the typhoid bacillus *Eberthella typhi*.

It has also been shown that, *in vitro*, mercurochrome is active against organisms of the colon-typhoid-dysentery groups and against *Vibrio comma*.

It has been possible to cure rabbits that had been made gallbladder carriers of *Eberthella typhi* by giving mercurochrome intravenously or by mouth.

CONCLUSION

In mercurochrome-220, a drug has been found which experimentally meets the requirements of a biliary antiseptic, in that it is excreted in the bile in bacteriostatic and bactericidal strength, and which, as has been previously shown, is of low enough toxicity to allow its safe clinical use intravenously or by mouth. The trial of mercurochrome clinically in both latent and acute gallbladder infections is not only justified but also clearly indicated from these experimental findings.

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BLOOD VOLUME

I A METHOD FOR DETERMINING WHOLE BLOOD VOLUME BASED ON
THE CIRCULATING CORPUSCLE VOLUME *

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A method is presented for determining whole blood volume by means of the circulating corpuscle volume. After a transfusion of unlike group blood, the transfused corpuscles can be separated from the recipient's corpuscles by agglutinating the latter with a serum of the same type as that of the blood transfused. If the transfusion is of blood of Group 1 (Group 4, Moss) into a recipient of Group 2, 3 or 4 (Group 1, Moss), the separation will be nearly quantitative. Since the amount of blood transfused is known, the degree of its dilution in the recipient may be determined and the blood volume calculated.

The method, which has already been noted,¹ is of interest because, owing to the simplicity of the procedure and to the stability of the unlike group blood in the circulation of the recipient, multiple determinations can be made over a considerable length of time. The method is a by-product of a purely therapeutic measure and inconveniences patients very little. In fact, the procedure is so simple that it would be feasible to run several daily blood volume determinations over a period of two or more weeks. Although the method, dependent as it is on corpuscle counting, does not have the degree of consistency of the dye method,² for instance, and is not preferred when that can be used, it nevertheless has the advantage that, since it affords an almost continuous picture of blood volume changes, the possibilities of blood volume behavior may be deduced from it, the verity of which may be checked at appropriate periods by some method mechanically more accurate. In other words, it may be used as a scouting measure, and on apparent blood volume changes of significance the finding can be substantiated by some other procedure, such as injection of vital red. It also has a certain theoretical interest in connection with the question of the equality of distribution of the corpuscles throughout the circulation. The error inherent to the technic is equivalent to that of the routine red cell count.

* From the Mayo Foundation

1 Ashby, Winifred. Some Data on the Range of Life of Transfused Blood Corpuscles in Persons Without Idiopathic Blood Diseases, *M Clin N Am* **3** 783-799 (Nov.) 1920

2 Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch Int Med* **16** 547-576, 1915

The method, which bears certain resemblances to that of Todd³ is as follows. A count of the cells in the blood to be transfused is made and the initial unagglutinability of the recipient's blood with Group 1 serum is tested by a method previously described,⁴ then the patient, who must be either in Group 2, 3 or 4 (Group 1, Moss) receives a transfusion of 500 cc., or more, of Group 1 (Group 4, Moss) blood. At any time within two or more weeks, if there does not appear to have been any elimination of the transfused blood, a count of the unagglutinable corpuscles in the patient's venous blood may be made, and from the degree of dilution of the transfused blood in the circulation of the recipient, the volume of the whole blood may be calculated using the formula,

$$V = \frac{C_t \times V_t}{U_2 - U_1},$$

V being the total volume, V_t the volume of the blood trans-

fused, C_t the count of the corpuscles in the blood transfused, and U_1 and U_2 the counts of unagglutinated corpuscles before and after transfusion. For obtaining the venous blood a small syringe containing a trace of dry citrate and fitted with a fine needle may be used without annoying the patient much more than would the ordinary ear puncture. One cubic centimeter of blood or less is sufficient.

The method is of theoretic interest because by means of it a whole blood volume may be derived, which depends on a corpuscle volume measurement, and also because this corpuscle volume measurement does not involve the noncirculating hemoglobin-like substance, as may occur with the carbon monoxid method. The whole blood volume derived from it should correspond to blood volumes obtained by the injection of a plasma soluble substance, except that the error due to irregularities in the relative distribution of plasma and corpuscles should, with this method, be exactly the converse of that involving the use of a serum soluble substance. That this method is based on a direct corpuscle volume determination appears readily on analysis.

It is assumed that the transfused blood corpuscles, $C_t \times V_t$, are evenly mixed with the circulating corpuscles of the recipient, but not necessarily evenly distributed throughout the circulation. Any sample of blood drawn should show the same ratio between the count of the transfused blood corpuscles and the red cell count as exists between the total number of cells injected and the total number of cells in the body. Therefore, $C_t \times V_t$, the number of cells transfused, divided by

³ Todd, C., and White, R. G. On the Fate of the Red Blood Corpuscles When Injected Into the Circulation of an Animal of the Same Species, with a New Method for the Determination of the Total Volume of the Blood, Proc Roy Soc, London **84** 255-259, 1911-1912.

⁴ Ashby, Winifred. Study of Transfused Blood, I, The Periodicity in Eliminative Activity Shown by the Organism, J Exper Med **34**:127-146 (Aug.) 1921.

$U_2 - U_1$, the number of the transfused corpuscles per unit volume of the recipient's blood, multiplied by C, the red cell count for a unit volume of the recipient's blood, determined from the same specimen as U_2 , gives the total number of corpuscles in the circulation. To obtain the total corpuscle volume, it is only necessary to know the volume of an average corpuscle, which can be derived by means of the hematocrit. If the recipient's cells are of a different size from those of the transfused blood, a correction could, of course, readily be made, as the relative numbers of transfused and native cells are known, no correction can, however, be made for any change in the size of the individual corpuscle which may occur as it passes to different parts of the circulation, where it is exposed to different tensions of carbon dioxide. If we proceed to obtain a figure for the total blood volume, the contribution of the hematocrit in determining the corpuscle volume will cancel out,⁵ therefore, all we really need to know is that as there are $\frac{C \times C_t V_t}{U_2 - U_1}$ cells in the circulation, and C cells in the unit of blood examined, assuming that the proportion between plasma and corpuscles is the same in the rest of the

body, $\frac{C \times C_t V_t}{U_2 - U_1}$ will give the number of those unit volumes which measure the total blood of the circulation. C cancels out, and the formula for the whole blood derived from the cell volume is $\frac{C_t V_t}{U_2 - U_1}$. Although, from

Let X^t be the volume of the corpuscles in 1 cmm of the blood transfused. Let X^p be the volume of the corpuscles in 1 cmm of the patient's blood before transfusion. Then $\frac{X^t}{C_t}$ and $\frac{X^p}{C_p}$ will equal the volume of an average corpuscle respectively of the transfused blood and of the patient's blood before transfusion. The hematocrit reading of the patient's blood

after the transfusion will be $\frac{\frac{X^t}{C_t} \times (U_2 - U_1) + \frac{X^p}{C_p} \times (C - [U_2 - U_1])}{1}$

and the average volume of a corpuscle in the patient's circulation after the

transfusion will be $\frac{\frac{X^t}{C_t} \times (U_2 - U_1) + \frac{X^p}{C_p} \times (C - [U_2 - U_1])}{C}$

Since the total number of corpuscles in the circulation are $\frac{C_t V_t}{U_2 - U_1} \times C$ the total corpuscle volume will be

$\frac{C_t V_t}{U_2 - U_1} \times C \times \frac{X^t}{C_t} \times (U_2 - U_1) + \frac{X^p}{C_p} \times (C - [U_2 - U_1])$

and the whole blood volume which is obtained by multiplying the corpuscle volume by 1 over the hematocrit reading, will be $\frac{C_t V_t}{U_2 - U_1}$

a casual consideration of the matter, it might seem that by substituting corpuscles for vital dye, I am simply introducing another method for measuring plasma volume, it will, I believe, be seen, on more careful consideration, that it is in reality a corpuscle volume method, as $\frac{C \times V_1}{U_2 - U_1}$, depends on the total number of corpuscles in the circulation, irrespective of their distribution.

LENGTH OF TIME THAT ALL THE TRANSFUSED CORPUSCLES REMAIN IN THE CIRCULATION

In any blood volume determination involving the injection of some substance distinguishable in the circulation, and the determination of its degree of dilution, the relative length of time before which an appreciable amount of the substance is lost from the circulation is a matter of importance. In my opinion, all the unlike group corpuscles, as a rule, stay in the circulation for from two to three weeks, sometimes longer. Apparently, they are in part eliminated by a certain physiologic state of the recipient, after which those escaping destruction remain in the circulation until removed by another crisis of elimination. The evidence for this conception has been given elsewhere.⁴ Although, in some patients, there is an initial fall in the count of the transfused corpuscles, there is reason to assume that it is due to an increase in the blood volume, and not to elimination of transfused corpuscles. These drops in the count have generally occurred either in patients who have received transfusions because of loss of blood and shock resulting from operation, and whose initial blood volumes have been low, as calculated by this method, or in patients with pernicious anemia whose first blood volumes have been low, but later, with evidence of improvement, have been apparently increased. Furthermore, the blood volume did not decrease beyond a point which would be consistent with dilution caused by the establishment of a probable blood volume as determined by the method of injection of vital red. As there were many instances in which the count of the transfused corpuscles was maintained at approximately the same level after transfusion, it would seem practically certain that when these initial drops in the count occur, they are due to blood volume adjustment, and that there is no elimination of the transfused corpuscles until one of these abrupt and marked changes in the count occurs. The findings in two cases of pernicious anemia that I have had the opportunity to study intensively for a long time are tabulated in Table 1. The constant counts for twenty-eight and thirty-one days, respectively, are shown, after which, within from two to three days, a fall occurred, and the count remained approximately constant at a lower stage for thirty-one days, in one instance, and for fourteen days, in the other, as long

as the patient was under observation. Determinations were made from blood taken from the ear.

TABLE 1—*Cases of Pernicious Anemia, Showing no Loss of Transfused Blood for a Month, with Subsequent Steplike Fall in Count*

Case 244, patient in Group 2 who received transfusion of 500 c.c. of Group 1 blood and Group 2 transfusion on the seventh, forty-ninth and fifty-fifth days after the Group 1 transfusion

Days After Transfusion	Total Red Cell Count	Count of Unagglutinated Corpuscles
0	3,080,000	615,000
3	2,990,000	616,000
6	2,810,000	629,000
8	3,280,000	621,000
11	3,220,000	698,000
13	3,430,000	702,000
15	2,990,000	631,000
17	3,050,000	621,000
19	3,140,000	644,000
21 (patient felt better)	2,920,000	593,000
22	2,770,000	616,000
24	2,940,000	638,000
26	2,780,000	623,000
27	2,940,000	597,000
31	2,940,000	652,000
34	2,820,000	451,000
36	2,750,000	557,000
38	2,800,000	542,000
56	3,180,000	518,000
58	3,480,000	509,000
60	3,260,000	467,000
62	2,990,000	467,000
64	3,300,000	519,000
68	3,300,000	479,000
69	3,080,000	451,000
71	3,010,000	428,000
73	3,110,000	372,000
75	3,010,000	377,000
77	3,210,000	385,000
79	2,920,000	421,000

Case 214, patient in Group 2 who received a Group 1 transfusion and five Group 2 transfusions while under observation

Days After Transfusion	Total Red Cell Count	Count of Unagglutinated Corpuscles
5	1,150,000	328,000
7	1,490,000	437,000
10	1,470,000	362,000
12	1,750,000	360,000
14	1,610,000	333,000
17	1,810,000	380,000
19	2,050,000	340,000
21	1,910,000	380,000
24	2,130,000	327,000
26	2,200,000	317,000
28	2,850,000	339,000
31	2,770,000	277,000
33	2,910,000	267,000
35	3,030,000	280,000
38	2,360,000	253,000
42	2,270,000	245,000
45	2,370,000	221,000

Wearn,⁶ however, who has used my method of determining the length of life of the unlike group transfused corpuscle, in a series of patients

6 Wearn, J. T., Warren, Sylvia, and Ames, Olivia. The Length of Life of Transfused Erythrocytes in Patients with Primary and Secondary Anemia, Arch. Int. Med. 29: 527-538 (April) 1922.

with pernicious anemia, and in another series with nephritis, considers that the transfused cells show a "steady gradual disappearance from the circulation of the recipient," but his data do not seem to me to support this conclusion. As he himself admits, the majority of his cases were observed at intervals too far apart to decide this point, then, too, the type of case chosen is one in which the vital red method has disclosed considerable capacity for volume variation. In the case of a patient with pernicious anemia, one of his most intensively studied cases, and one in which the transfusion was sufficiently large so that the fluctuations in the count of transfused corpuscles would not be within the error of the technic, there was a very definite indication of the steplike progress of elimination. Six hundred cubic centimeters of Group 1 (Group 4, Moss) citrated blood was transfused into a patient in Group 2, immediately afterward, the count of unagglutinable corpuscles was 530,000, while that taken thirty-one days later was 553,850, forty-eight days after transfusion, the count was 349,800, and fifty days after this reading, during which time certain irregular changes in the count occurred, one of which was, I believe, due to icebox incubation, the count was 351,450. Similarly in Case G, the first count of unagglutinable corpuscles, taken two days after transfusion, was 253,000, twenty-eight days after transfusion, it was 265,650. The next count, taken three days after this, was 163,350, that eighteen days later was 130,550. In Wearn's two cases of pernicious anemia, B and C, there was an initial fall of the count, which, judging from the amount of blood injected and the degree of the fall, might well have been due to improvement in the blood volume, as afterward the counts stayed on a level for considerable time. Of his nephritis cases, Case H would seem to me to be the only one that offers any evidence of continuous elimination of the transfused blood corpuscles, and, according to the protocol, there was a continuous loss of blood in the urine, which, in the course of sixty days, may have been sufficient to affect the number of transfused corpuscles. However, the amount of blood transfused, 250 c.c. diluted with citrate solution, was so small that it would be unwise to place much significance on the counts of transfused blood. His most significant case was Case A, because it was the most intensively studied and because a larger amount of blood was given, and yet this case does not substantiate the contention of a continuous and gradual elimination. If, as I believe, none of the transfused corpuscles, as a rule, leave the circulation for from fourteen to twenty or more days, this method is good for a prolonged study of blood volume changes. When doubt arises as to whether elimination of transfused corpuscles or increase in blood volume has occurred, the point must be checked by the parallel use of another method.

CONSISTENCY OF THE AGGLUTINABILITY OF THE
RECIPIENT'S CORPUSCLES

As this blood volume method is designed to be used over a considerable length of time, besides knowing something about the probability of elimination of the transfused blood, it is also necessary to know the probabilities of any change occurring in the agglutinability of the corpuscles of the recipient. The completeness of agglutination of the

TABLE 2—*Effect of Change in Concentration of Corpuscles on Unagglutinable Residue, U_1 , of Pure Agglutinable Blood Sample, the Same Agglutinating Serum Being Used for all Bloods*

Blood Showing No Effect of Concentration of the Corpuscles on U_1	Degree of Dilution		Count of Unagglutinated Corpuscles in 1 Mm	Original Count of Blood
	Blood	Serum		
Blood 1	1	55	2,050	1,770,000
	2	55	2,050	
	4	55	2,250	
	5	55	2,500	
Blood 2	2	55	1,800	1,510,000
	5	55	2,150	
Blood 3	1	55	550	4,500,000
	2	55	600	
	4	55	550	
	6	55	500	
Blood 4	1	55	1,300	5,000,000
	2	55	800	
	4	55	1,350	
	6	55	1,300	
Blood 5	1	55	2,000	5,390,000
	2	55	1,600	
	4	55	1,600	
	6	55	1,700	
Blood Showing an Effect of Concentration of the Corpuscle on U_1				
Blood 6	1	55	600	4,480,000
	2	55	1,500	
	4	55	2,800	
	6	55	5,600	
Blood 7	2	55	1,700	2,240,000
	5	55	5,600	
Blood 8	2	55	3,850	3,800,000
	5	55	6,500	

recipient's corpuscles depends partly on the potency of the serum used, and partly on a quality inherent to the corpuscles. Certain serums will agglutinate pure blood of an agglutinable type with a smaller residue of free corpuscles than will others. The potency of the serum can readily be checked, and, as iso-agglutinins are quite stable, it is often possible to use the same serum throughout a series of experiments. The possibility of change in the agglutinability of the recipient's corpuscles, however, called for investigation. It was necessary to know whether, as a result of a change in the condition of the patient, any change in the agglutinability of his corpuscles occurred, and also what error was introduced on an improvement or drop in his cell count by the increase or decrease in the number of his corpuscles, or, which involves the same point what correction should be made for the unagglutinable count of the

patient's own corpuscles, U_1 , when because of too great a density of the transfused corpuscles for convenience in counting, a further dilution with serum is necessary.

It would appear from a study of the unagglutinable residue of blood unmixed with corpuscles of an unagglutinable type that the agglutinability of the recipient's corpuscles is peculiar to the individual; it may change, but usually does not even in as long a period as a year, and that for the majority of bloods the number of cells free after agglutination does not depend on the density of the suspension agglutinated.

In five instances (Table 2), on varying the amount of blood agglutinated with a given amount of serum, the number of free corpuscles remained the same. The mechanism suggested, in these cases, was that which determines the dissolved fraction of a comparatively insoluble salt in the presence of an excess, rather than the differential agglutination of the more agglutinable corpuscles of a not entirely homogeneous mixture. In three bloods, on the other hand, this was not the case. These bloods, which, compared with the others, gave a high count of unagglutinable corpuscles, showed a variation in the number of free corpuscles as the amount of blood per unit volume of serum was changed. This may have been due to the presence of unagglutinable cells, of which there were more in the richer mixtures of blood, as suggested by the work of Isaacs,⁷ but as I have not found the cells described by Isaacs to be unagglutinable by my technic, I consider it more likely that the corpuscles, in these instances, were uniformly weakly agglutinable to such a degree that the mechanical manipulation necessary for making the count became a factor and loosened a greater number in the specimens with more clumps present. The findings are listed in Table 2.

Of twelve subjects whose blood was studied for agglutinability over intervals ranging from one day to a year, nine showed a consistency in the count of unagglutinated corpuscles which came within the error of the technic. The majority of these were patients with pernicious anemia, receiving a series of transfusions, one was a normal donor whose blood was tested before hemorrhage, and three days later. Of the three patients who showed variation, the blood of Mrs. S., which had a high count of unagglutinable corpuscles, showed an increase in agglutinability when the patient had an attack of pneumonia, with a return toward the high count on her recovery. The two marked exceptions were found in two patients whose counts were taken simultaneously a month apart; in one of these, there was an increase in the count of unagglutinable corpuscles, and in the other a decrease (Table 3).

⁷ Isaacs, Raphael. Properties of Young Erythrocytes in Relation to Agglutination and Their Behavior in Hemorrhage and Transfusion, Arch. Int. Med. 33: 193-209 (Feb.) 1924.

The practical result of these observations is that, after an unlike group transfusion, the probabilities are that the agglutinability of the recipient's corpuscles will not have changed, and that a true figure for the number of unagglutinable corpuscles introduced by the transfusion will be obtained by subtracting the count of unagglutinable corpuscles made

TABLE 3.—*Illustrations of Degree of Stability of U₁, Residue of Unagglutinated Corpuscles of an Agglutinable Blood, Observed in Patients Over Varying Lengths of Time When Group 1 Serum Was the Agglutinating Medium*

Case	Date	Red Cell Count	U ₁	Notes
23	1/ 4/19		80,000	
	12/ 8/19	830,000	70,000	
97	10/ 7/19	1,900,000	70,000	
	4/ 2/20	2,080,000	87,000	
	9/ 2/20	2,240,000	70,000	Splenectomy, Aug 5, 1920, followed by transfusion
155	5/ 9/21	1,480,000	18,700	Patient in Group 4, receiving Group 2 trans
	5/16/21	2,380,000	14,000	fusions
Dr W	2/24/20	4,290,000	71,000	
	2/26/20	4,120,000	62,000	
	2/28/20	3,450,000	66,000	
	3/ 3/20	3,450,000	71,000	
	3/ 5/20	2,720,000	74,000	
J H	2/ 8/21	1,160,000	55,000	Before transfusion
	2/ 8/21	1,890,000	58,000	After transfusion
	3/ 2/21	1,810,000	43,000	
	3/ 3/21	1,760,000	49,000	
Mrs B	2/ 4/21	1,920,000	53,000	Before transfusion
	2/ 4/21	2,090,000	40,000	After transfusion
N	2/20/24	1,510,000	47,000	Receiving a series of transfusions
	3/21/24	1,980,000	69,000	
A	2/20/24	2,240,000	102,000	Receiving a series of transfusions
	3/21/24	3,510,000	113,000	
Mrs S	2/ 4/21	1,810,000	101,000	Before transfusion
	2/ 4/21	2,360,000	98,000	After transfusion
	2/ 7/21	2,330,000	76,000	
	2/13/21	2,280,000	96,000	
	2/14/21	1,890,000	50,000	
	2/15/21		45,000	Had pneumonia
	2/26/21	3,250,000	77,000	
J C	2/26/21		28,000	
	2/29/21		11,000	Professional donor Three days after loss of 500 c.c. of blood
C	2/20/24	3,810,000	128,000	
	3/21/24	3,910,000	79,000	
B	2/20/24	1,770,000	40,000	Transfusions
	3/21/24	2,890,000	102,000	

by the same technic before transfusion from the count of unagglutinable corpuscles made after transfusion. If, in the meantime, the patient's blood count has changed, the probabilities of error will be less, if no account is taken of the change in making allowance for the native unagglutinable cells. When, because of too great a density of the transfused unagglutinable corpuscles, it is difficult to make the count and it becomes necessary to dilute the specimen, as taken by the usual technic, with serum, before subtracting the initial count of the recipient's unag-

glutinated corpuscles from the total count, the initial count should be multiplied by the amount of the dilution of the specimen

A COMPARISON OF COUNTS MADE ON BLOOD FROM THE EAR AND FROM THE VEIN

In a series of comparisons of red blood counts made from the ear and from the basilar vein, it was found that the counts of blood from the ear might be higher or equal to the counts from the vein, but that they were usually higher, very exceptionally were they lower. This was true in normal subjects and in patients with pernicious anemia. The range in the absolute difference in the counts in the patients with pernicious anemia was equal to that in the normal subjects, being from 0 to about 80,000 corpuscles for each cubic millimeter of blood, the percentage difference in the patients was, of course, because of the low red blood counts, very much greater in this group. The fact that the range of absolute difference is similar in the two groups suggests that this increase in the capillary count over the venous count may not be a function of the blood, for if the difference were due to a change in the proportion of corpuscle and serum, it would be much greater in the normal blood. It would seem probable that it is a function of something which is more equal in the two types of cases. This common factor is likely to be capillary volume. It seems to me that on cutting tissue, certain of the capillaries may go into the expanded condition of shock and permit the passage of fluid through their walls, thus becoming packed with corpuscles, as described by Krogh⁸. The slight milking, employed to obtain the drop of blood for the count, would be expected to dislodge these and increase the count taken from such a cut over that taken from the vein. The fact that duplicate counts from the ear have proved to be more irregular than can be explained on the basis of error in the technic of dilution and counting, as judged from the percentage of error found in the work of the same technician in duplicate counts of citrated blood, would seem to indicate that the error lies in the process of obtaining the blood. Since I believe it highly probable that a count of blood taken so that it includes blood obtained from injured capillaries may not be a true index of the corpuscle content prior to injury, I consider it very desirable to obtain the count from venous blood.

SUMMARY AND CONCLUSION

A method for determining blood volume is described, based on the degree of dilution of transfused Group 1 (Group 4, Moss) blood in a recipient of another group.

⁸ Krogh, A. The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922.

It is shown that the whole blood volume obtained by this method is dependent on circulating corpuscle volume. On this account, the results obtained by it would constitute a check on whole volume calculations based on plasma volume determinations.

The method is advocated as a means of studying blood volume changes.

ASTHENIA AS A CHIEF COMPLAINT IN CARCINOMA OF THE STOMACH*

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That the subject of gastric carcinoma is a paramount one must be evident to all. About one half of all cancers occur in the stomach. Martin¹ found that 0.47 per cent of all hospital admissions are for gastric cancer. Ewing² similarly emphasizes the great frequency of this tumor. "The stomach is probably the most frequent seat of cancer in the male, as the uterus is in the female." Whether the condition numbers one third or one half of all neoplasms is not essential, but it does demonstrate the tremendous importance of early recognition. Modern medicine and surgery avail little. Whereas our laboratory aids have advanced, our clinical intuition has lagged behind, and so we find that the diagnosis of gastric carcinoma is still terribly hopeless. Hence, any clinical means that may aid the internist or laboratory man in making an earlier diagnosis must be of distinct value.

In the study of this subject, one finds that the usual textbook descriptions have been handed down from author to author. Similarly, the clinician in the diagnosis of peptic carcinoma keeps in mind the picture of an old man with a palpable tumor, cachectic, vomiting and with anacidity.

Before these symptoms and findings become outstanding, there must have been a period of growth when there were none or, at the most, few symptoms, so, too, before the roentgenologist finally examines the patient and discovers a large defect, there must have been a time when a small lesion was present. It is with the hope that carcinoma of the stomach will be suspected earlier in certain types of cases that this paper is presented. The type referred to is the case in which gastro-intestinal symptoms are entirely lacking, or, if present, occur to a minimal degree. In fact, one can usually obtain more or less indefinite gastro-intestinal complaints in any individual between 40 and 60, especially if he is ill. The patient who has gastro-intestinal complaints in the foreground is the classical type, the one described in books and taught in the medical school. It is the other type, less frequent, more difficult of recognition but none the less important, with which we are concerned. In fact, one author¹ goes so far as to state, "One general rule holds in

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1 Martin C F Carcinoma of the Stomach, in McCrae, Osler, Modern Medicine 3 264

2 Ewing Carcinoma of the Stomach, in Neoplastic Diseases, Ed 2, p 624

most cases, viz., the absence of all gastric symptoms and signs is important evidence against cancer." With this statement the facts of this paper differ entirely.

The following is the first case of gastric carcinoma in which the history revealed absolutely no gastric symptoms and in which weakness was the chief complaint or signal symptom.

CASE 1.—A Russian, aged 56, married, a waiter, was admitted, Jan 5, 1922, and discharged January 25, with the diagnosis of carcinoma of the stomach (inoperable). The condition was unimproved.

His chief complaint was weakness, which had persisted for the last six months. He had been told some time previously that he suffered from kidney trouble. However, he had no dysuria, no nocturia or hematuria, only frequency. His present illness commenced about six months before admission, with a feeling of weakness. This weakness progressively increased until about one week before admission, when it became so marked that the patient was forced to discontinue work and go to bed. No gastric symptoms, no nausea or vomiting and no jaundice were present. His appetite was fair, he was mildly constipated. He never noticed bloody or tarry stools, and there was no known loss of weight.

Physical examination showed a poorly developed and poorly nourished middle aged man. Physical examination was negative, except for a marked, yellowish pallor of the mucous membranes and the skin. A small, lipomatous mass was found near the left nipple. The deep reflexes were hyperactive.

Because of the pallor, complete routine blood tests were performed. The bleeding and coagulation time were normal. The blood count showed 52 per cent hemoglobin, 3,160,000 erythrocytes (0.83 color index), 10,000 leukocytes, 72 per cent polymorphonuclears, 18 per cent lymphocytes, and 10 per cent monocytes. Slight anisocytosis and poikilocytosis of red cells were present. Blood platelets numbered 106,000. The blood pressure was 145 systolic, 65 diastolic. The Wassermann test was negative. The phenolsulphonephthalein test resulted in the return of 24 per cent dye excretion in two hours. The stools were found positive for occult blood. The roentgen-ray examination of the gastro-intestinal tract showed evidence of a neoplasm on the posterior wall and lesser curvature, just below the cardia. It seemed quite extensive. The pyloric half of the stomach showed no abnormality. Peristalsis in the area was normal. Surgeons considered the case inoperable.

Apparently, the cardia and pyloric orifices were patent, peristalsis was normal and no retention was present, hence, there were no gastric symptoms. This is the usual type in which weakness is the chief complaint, and in which gastro-intestinal symptoms are entirely absent or negligible.

The second patient was a man who entered the hospital for an acute inflammatory condition of the eyelid, but whose fundamental complaint was weakness.

CASE 2.—A peddler, single, admitted, May 15, 1923, and discharged, August 22, with the diagnosis of carcinoma of the stomach, was admitted to the eye service with a complaint of pain and swelling about the right eye which he had had for eight days. He had had gonorrhea fifteen years before, with a "touch of chancre" at the same time. For six months, he had been feeling weak and run down, and occasionally suffered from dizzy spells.

Physical examination showed an acutely ill man, aged about 45, with lemon colored skin and swelling and redness of the right eye, the lids being almost closed. Red streaks extended along the forehead. The optic nerve heads were pale. The teeth were in poor condition. The tongue was glossy, smooth and atrophic. A large "spleen" was palpated in the left hypochondrium, four fingers below the costal margin, extending to the epigastrium.

The provisional diagnosis was orbital cellulitis with spreading lymphangitis (cavernous sinus disease? tabes?)

The right upper and lower lids were incised, and pus was evacuated. The visual fields were found to be normal. The blood pressure was 110 systolic, 55 diastolic. A diagnosis of splenomegalic cirrhosis was made because of the large liver and spleen. The glossy tongue was ascribed to syphilis.

The patient was transferred to the medical side of the hospital. The blood count was 34 per cent hemoglobin, 3,184,000 red blood cells (0.53 color index), 19,200 white blood cells, 68.5 per cent polymorphonuclears, 2.5 per cent eosinophils, 0.5 per cent basophils, 20 per cent lymphocytes, 7 per cent monocytes, and 1.5 per cent myelocytes. The blood platelets totaled 450,000. The stool was positive to the quaiac test for blood. No free hydrochloric acid was found in the fasting or the Ewald test meals. The urine was constantly negative. The blood and the spinal fluid Wassermann tests were negative. The roentgen-ray examination of the stomach showed the presence of a large defect, involving almost the entire upper two thirds of the stomach. This observation indicated the presence of a new growth.

The third case was that of a man whose first discharge diagnosis was atheiosclerosis and whose chief symptoms were weakness, chest pain and dyspnea, with no or only negligible gastric complaints. He was discharged improved, and then returned. No one suspected a gastric condition.

CASE 3—A Russian, aged 52, a tailor, was admitted Dec 3, 1923, and discharged December 20, with a diagnosis of carcinoma of the stomach. His chief complaint was weakness, which had persisted for nine months. The patient had always been healthy until nine months before, when he suddenly fell unconscious while walking in the street. After this, he remained in bed for nearly two months because of weakness. This weakness increased so that, for six months, he could not walk. On attempting to walk, he became very pale, complained of precordial distress and felt as though he were about to die. For the previous five months, he had had constant pains all over the abdomen, this pain bore no relation to meals, and was relieved somewhat by bowel movement. During this time, he was slightly constipated. Seven months before, he had had gaseous eructations, and had vomited. The stools were normal in color, there was no hematemesis, no jaundice. His appetite was poor, and he had lost much weight. Physical examination showed him to be an underdeveloped, undernourished old man, chronically ill, yellow, with an edematous sacrum and scrotum. The pupils were slightly irregular, a marked arcus senilis and tortuous blood vessels were present. The supraclavicular fossae were sunken. The heart was moderately enlarged to the left, with a low pitched, blowing, presystolic, systolic murmur at the apex and mitral area. The blood vessels were thickened. Liver dulness was increased.

The systolic blood pressure was 120, the diastolic, 60. The stools showed occult blood. The blood count was 38 per cent hemoglobin, there were 3,000,000 erythrocytes (0.63 color index), 13,000 leukocytes, 85 per cent polymorphonuclears, and 15 per cent lymphocytes.

Gastric analysis showed absent hydrochloric acid and diminished total acids in the fasting and Ewald test meals. The urine was negative except once, when a trace of sugar was found. Roentgen-ray examination of the gastro-intestinal

tract showed the gastric tone and peristalsis to be normal. There was a suspicion of a small defect on the posterior wall in the region of the cardia, just to the left of the cardiac opening. Sigmoidoscopy, December 17, revealed an obstructive extracolonic mass at the level of the second fold of Houston. The final diagnosis was carcinoma of the cardia with metastases to the peritoneum and to the culdesac of Douglas in a patient previously discharged from the hospital with a diagnosis of arteriosclerosis, and who had returned to the hospital because of weakness.

These three cases led to an investigation of the cases of carcinoma of the stomach on the medical side for the years 1923, 1922 and 1921, in which there were, at the onset or throughout the course of the case, no gastro-intestinal complaints, or in which these were in the background. Asthenia was a complaint months before a diagnosis of gastric cancer was made.

CASE 4—A patient, aged 60, examined, July 10, 1923, had as chief complaint weakness of two years' duration, his symptoms, for the previous two months had been aggravated by coughing. Swelling of the ankles was noted. The laboratory findings, i.e., the Ewald test meals and the roentgen-ray examination, were characteristic of stomach carcinoma. A defect was found in the posterior wall and along the lesser curvature of the body of the stomach.

CASE 5—A man, aged 44, was in perfect health until a few months previous to June, 1923, when he lost appetite and strength. He had no other gastro-intestinal symptoms. The case had been diagnosed as neurasthenia and over-work, and he had been sent to Florida. An exploratory laparotomy disclosed an inoperable cancer of the stomach with liver metastases.

CASE 6—A man, aged 62, was absolutely symptomless until two days before admission in September, 1923, when he entered the hospital because of a hemorrhage and weakness. Roentgen-ray examination gave evidence of a small defect on the posterior wall of the stomach in the region of the cardia.

CASE 7—A man, aged 64, whose signal complaint was increasing weakness for three months, had lost 35 pounds (15.9 kg) and complained of anorexia, belching and a feeling of distention after meals. The case was signed out as an inoperable carcinoma of the stomach on the greater curvature.

CASE 8—A man, aged 58, whose chief complaints were weakness, dyspnea and swelling of the feet of five weeks' duration, entered in March, 1922. No loss of appetite, no vomiting, no bleeding and no abdominal pain were present. A fairly large defect on the lesser curvature below the cardia was found.

CASE 9—A man, aged 59, examined in September, 1923, had had increasing weakness for two months. The roentgen-ray examination showed a large defect in the greater curvature of the stomach.

CASE 10—A man, aged 56, whose first symptom was extreme weakness that had commenced one year previous to admission, in January, 1922, and which was associated with anorexia, had lost 28 pounds (12.7 kg) in the course of the year. There were no gastro-intestinal symptoms except constipation. A subtotal gastrectomy was performed, and the patient was discharged well.

CASE 11—A woman, aged 56, whose signal symptom was weakness for six months, was admitted in January, 1923. The weakness grew progressively worse. Other complaints were palpitation, precordial pain, dyspnea and pallor. She lost about 10 pounds (4.5 kg). The case was diagnosed as secondary anemia and nephritis. The Rehfuss test showed no free hydrochloric acid, and the roentgen-ray examination demonstrated irregularity in the region of the antrum.

CASE 12—A woman, aged 55, who eight months before admission, in January, 1921, began to feel weak, was without definite symptoms until four months previous to admission, when she commenced to cough, developed pain in the back, and had dysphagia A carcinoma of the cardia was found

CASE 13—A woman, aged 50, who lost 50 pounds (22.7 kg) in five years and whose strength had greatly diminished, was admitted in June, 1921 Her complaints were cardiac, i e, palpitation and precordial pain There were no tarry stools, jaundice, belching or pyrosis The Rehfuss test showed blood and an absence of hydrochloric acid There was no roentgen-ray confirmation in this case

CASE 14—A woman, whose chief complaint was gradual weakness of two months' duration, but who had had a sour taste in the mouth for four months, was admitted in October, 1921 There was no vomiting, belching or bloody stools The bowels were regular Free hydrochloric acid was absent in the test meal No roentgen-ray confirmation was made and the patient left the hospital against advice

CASE 15—A man, aged 64, who eight months previously had noticed swelling in the feet and progressive weakness, was admitted in September, 1921 The Rehfuss test proved the absence of free hydrochloric acid and the presence of lactic acid Roentgen-ray examination showed a defect involving the pyloric end of the stomach

COMMENT

Here is a series of seventy-six medical cases of carcinoma of the stomach in which fifteen patients, or 20 per cent, complained chiefly of asthenia and presented no, or a very mild, gastro-intestinal history If we exclude Cases 13 and 14, in which absolute confirmation of the diagnosis is lacking, we still find a record of 17 per cent It is true that the cases were not the type that the surgeon sees, i e, the typical patient, almost cachectic, with all the classical signs of cancer They were cases chiefly sent in for diagnosis

The complaint of asthenia so common here was not the asthenia of cachexia That symptom, of course, would be worthless On the contrary, the complaint was comparable to asthenia of early pulmonary tuberculosis

Patients with cancer of the breast, uterus, esophagus or lung do not complain chiefly of weakness Apparently, it is characteristic in the cases under discussion

As to the cause of the asthenia, a secondary anemia is common in cancer of the stomach In fact, extremely important differentials are pernicious anemia, secondary anemia and nephritis A destruction of the red blood cells occurs, probably due to a toxic agent set up by the neoplasm (one author³ has suggested that protein and lecithin cause this) The asthenia may directly, rather than indirectly, be due to the infection and ulceration of the tumor In fact, both the latter conditions

³ Loeper, M., Faroy, G., and Debray Anemia with Gastric Ulcer, Progrès med 36 244 (May 25) 1921, abstr J A M A 77 579 (Aug 13) 1921

are quite common in the lesion described. Many authors⁴ have noted the simulation of pernicious anemia with symptoms of weakness, numbness and tingling hands and feet and other paresthesias.

The lack of gastro-intestinal complaints can probably be explained on the basis of the location of the growth. When the pyloric and cardiac orifices are involved, gastric complaints are prominent because of obstruction. Some authors even divide "early gastric cancer" into those in which the cancer is situated near the orifices and those that are not. Brown⁵ states that the most frequent site is the lesser curvature from whence the growth extends to pyloris, cardia or over the fundus of the stomach. The same author also described three types of gastric carcinoma, one of which is insidious in onset and affects persons of middle life with a singularly uneventful digestive history.

Smithies,⁶ in 712 consecutively operated and pathologically proved cases, found that 2 per cent gave no symptoms whatever.

SUMMARY

In a condition like carcinoma of the stomach, in which the early symptoms are vague and in which, unfortunately, an early diagnosis is extremely essential, one must utilize every means at his command. Not the least of these is the history obtained from the patient.

Asthenia as a signal complaint is not an uncommon symptom of tumor of the stomach, being present in from 17 to 20 per cent of this series of (medical) cases.

Absence of gastro-intestinal symptoms does not rule out carcinoma of the stomach. The presence of asthenia and anemia, with absence of gastro-intestinal symptoms in a middle-aged person with no apparent cause for the anemia, is an indication for gastro-intestinal roentgen-ray examination. In fact, on this complaint alone, if no cause for the severe secondary anemia can be found, an exploratory laparotomy should be performed. Anemia, secondary or even primary, is a diagnosis which should immediately bring to mind a possible differential diagnosis of carcinoma of the stomach. The anemia, when present, is probably due to destruction of the red blood cells by a substance produced by the new

⁴ Ohensis, A. E. Carcinoma of the Stomach Simulating Pernicious Anemia, New York M. J. **114** 298 (Sept 7) 1921. Houghton, Hallstead and Satterlee. Progressive Pernicious Anemia with Gastric Carcinoma, Long Island M. J., October, 1914, p 361.

⁵ Brown, T. R. Carcinoma of the Stomach, Nelson System of Medicine, **5** 295, 1924.

⁶ Smithies, Frank. Symptoms and Signs of Gastric Cancer, An Analysis of 712 Consecutive Operatively and Pathologically Proved Cases, J. A. M. A. **64** 8 (Feb 20) 1915.

growth. The asthenia is due to this anemia, or to the toxic products caused by the infection and ulceration of the growth.

The practically constant subacidity, an acidity or achylia suggests that the absence of the gastric secretions plays an important rôle in the anemia, and hence the complaint of weakness. The association of the same findings in pernicious anemia adds interest to this suggestion.

Cases were presented in which the symptom of weakness preceded by months or years the diagnosis of cancer of the stomach.

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CORRECTION

"The Permeability of Human Blood Cells to Carbon Dioxide and Ammonia Hydroxid in Solutions of Same p_{H_2} ," Herman E. Pearse, A.B., Boston, March issue, p. 347. The word "later" in the third line should read "latter."

Book Reviews

THE CHEMISTRY OF THE BLOOD IN CLINICAL MEDICINE By O L V DE WESSELOW Pp 252 London Ernest Benn, Ltd, 1924

This manual discusses the chemical composition of the blood, acidosis and alkalosis, variations of the blood sugar in health and disease, changes of the blood constituents in nephritis, tetany, rickets, gout, and in certain other conditions, such as anoxemia

To these discussions are added methods for determining the nonprotein nitrogen constituents of the blood, the chlorids, the carbon dioxid combining power of the plasma, the phosphate and calcium content

Although the methods given are excellent and the subject matter is well presented, most of these are contained in other more comprehensive laboratory guides

PATHOGENIC MICROORGANISMS By PARK and WILLIAMS Eighth edition, enlarged and revised Pp 811, 220 illustrations Price, \$6 50 New York Lea and Febiger, 1924

To the students of bacteriology this text needs no introduction. It ranks among the foremost of its kind, and this edition has been brought to date by thorough revisions and extensions. The essential features of bacteriology, the preparation and sterilization of mediums, the characteristics of various pathogenic bacteria, immunity, the protozoan parasites, water and milk sanitation, filterable viruses, and other important features in the realm of bacteriology are fully and excellently discussed. Students and workers in bacteriology will find this an invaluable text

THE CHEMICAL ASPECTS OF IMMUNITY By H GIDEON WELLS Monograph (American Chemical Society Series) Pp 254 New York Chemical Catalog Company, Inc, 1925

This monograph by Wells has been written not only with the purpose of summarizing the subject matter included by the title but also for serving as a guide to the literature concerned. The introductory chapter states the reasons for regarding immunologic reactions as chemical processes, and defines briefly the terms commonly used. Then follow chapters on antigens, immunologic specificity, the nature of antibodies, the neutralization of toxin by antitoxin, agglutination and precipitation reactions, the lytic reactions, the Wassermann reaction and related reactions with syphilitic serum, anaphylaxis, phagocytic immunity, and resistance to nonantigenic poisons. Each chapter is a concise resume, and includes a large bibliography. A helpful recapitulation by the author summarizes at the end of each chapter the subject matter presented. Dr. Wells' fine ability to analyze and present a subject such as this makes the monograph especially fascinating to read, and the book should be in great demand by immunologists, chemists and physicians.

PRINCIPLES OF BIOCHEMISTRY By T BRAILSFORD ROBERTSON, PH D, D Sc Second edition, revised Price \$8 50 Pp 796, 57 illustrations New York Lea and Febiger, 1924

This text is arranged in six parts. Part I considers the foods, such as the inorganic substances, the carbohydrates, the lipins, the simple and complex proteins, and the hydrolysis, digestion and assimilation of these substances. This part contains much information. The properties of protoplasm are dis-

cussed in Part II. In these chapters are considered the diffusible and colloidal constituents, the physical and chemical properties conferred by these constituents, their variations and interactions. In Part III is considered the chemical correlation through the blood and lymph of the respiratory, digestive and circulatory systems, as well as the general metabolism. Part IV deals with the chemical processes underlying and accompanying life phenomena, such as the energy transformations in living organisms, fertilization and early development, growth, diet, etc. The products of tissue activity are discussed in Part V, and the energy balance of the organism in Part VI.

There is a great diversity of subjects considered in this text of biologic chemistry. To students of medicine, of agriculture and related sciences, as intended, this is a valuable text but it does not contain the large volume of detailed information present in certain other books of this kind, as, for example, the one by Mathews or the one by Hammarsten.

LES RÉSULTATS DU PNEUMOTHORAX THÉRAPEUTIQUE By DR PIERRE NAVEAU
Pp 199 Paris Amedee Legrand, 1925

This is a statistical review of the results observed during a period of twelve years in 1,195 patients (service of Dr Rist). In 817 of this number, pneumothorax was produced, with the other 378, the attempted collapse of the lung was unsuccessful, or the patients refused the treatment. There is no description of the technic employed. The patients treated are arranged in two groups, those nontuberculous and those tuberculous. Among the first mentioned are those with bronchiectasis, gangrene of the lungs, and interlobar or pulmonary abscess. The results among these seem good except with gangrene. With tuberculous patients, pneumothorax favors healing of the pleura. In bilateral tuberculosis, only a small number were benefited. The treatment seems to be helpful when only one lung contains active lesions. Of 534 patients with fibrocaceous tuberculosis, 48 per cent are well or improved, 17 per cent are stationary, and 35 per cent are worse or dead. Among the patients in whom pneumothorax was not accomplished, 81 per cent of those refusing treatment and 62 per cent of those in whom adhesions prevented collapse are dead. Considerable space is given to detailed clinical briefs of patients.

THE DIAGNOSIS AND TREATMENT OF RENAL DISEASES By HUGH MACLEAN,
M.D., D.Sc. Second edition Philadelphia Lea and Febiger

According to the author's preface, the book "is intended principally for the general practitioner who feels the need of a short practical account of some of the newer methods employed in investigating renal function." The author has accomplished his purpose in a clear, concise and interesting manner. He is in an unusual position to do this since he has the point of view both of the investigator and the clinician of vast experience in this special field.

The accepted theories of renal function are discussed in relation to the actual findings in acute nephritis and in chronic nephritis, both of the azoemic and the hydremic types. Along with the changes in the urine, blood and tissues are given the findings relative to nitrogen, salt and water retention.

Histologic observations are presented and illustrated by colored plates. The significant remark is made "that the toxin causing the purely degenerative lesion of the kidney (tubular degeneration and hydremic type) may be different from that causing degeneration associated with inflammatory phases (interstitial changes and azotemic type)."

A chapter is devoted to the significance of albuminuria in which the differentiation is made between so-called physiologic albuminuria, albuminuria of adolescents and albuminuria of nephritis. In regard to the last, the statement is made that albuminuria even with casts may not indicate kidney disease, and that albuminuria even after acute nephritis may not indicate progressive renal disease.

The methods and results of blood examinations in renal disease are given in a manner easily understood and readily employed by any enterprising physician. Then other tests for investigating renal function follow—the urea concentration test, the diastatic test, the phenolsulphonephthalein test, Ambard's coefficient of urea excretion, the urea concentration factor, and the chlorid concentration test.

The later chapters concern themselves with the relation of nephritis to blood pressure and cardiovascular changes, the examination of patients for renal efficiency, kidneys in surgical conditions, and the dietetic treatment of nephritis (especially as regards protein).

Archives of Internal Medicine

VOLUME 35

MAY, 1925

NUMBER 5

EFFECT OF VARIOUS AGENTS — ULTRAVIOLET LIGHT, VACCINES, TURPENTINE, NEOARSPHEN- AMIN AND AUTOBLOOD INJECTIONS — ON THE ENZYMES OF BLOOD AND SKIN *

A PRELIMINARY REPORT

JAY FRANK SCHAMBERG, M.D.
AND
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Within recent years, many physical agents and various nonspecific protein injections have been advocated in the treatment of cutaneous diseases and in other general morbid conditions. The roentgen rays and ultraviolet light have been employed in many skin diseases and, likewise, in tuberculosis, cancer, leukemia and other diseases. Vaccines, both specific and nonspecific, have been extensively used in many infections. Oil of turpentine has been employed to raise the resisting power of the organism in pyogenic conditions. Autoserum and autoblood injections have been successfully employed in psoriasis and in certain other dermatoses. Many other nonspecific protein injections have been credited with desirable therapeutic effects.

In view of the free employment of these various agencies we have thought it worth while to endeavor to study the influence of some of them on that relatively little explored field, the enzymes of the body. We have largely limited our investigations to a study of the lipase and protease in the blood and in the skin.

The lipase determinations were numerically greater than the protease for the reason that, to obtain a sufficient quantity of blood for the latter, the laboratory animal had to be sacrificed. It was obviously impossible, with the method employed by us, to make comparative studies of the skin enzymes before and after treatment, as this could be determined only after the death of the animal.

EFFECT OF ULTRAVIOLET LIGHT

Ten rabbits were, at various times, exposed to ultraviolet light (Alpine lamp). The rabbits weighed about 2 kg. These were usually

* From the Research Institute of Cutaneous Medicine

exposed at a distance of 10 inches (25.4 cm.), in such a manner as to permit irradiation of the greater part of the body. The exposure was usually twenty minutes. Many of the animals were exposed a second, third, fourth and fifth time, at intervals of a few days.

TABLE 1.—Effect of Ultraviolet Light on Blood Serum Enzymes of Rabbits
(Alpine Lamp)

Rab- bit	Treatment	Blood		Skin			Remarks
		Proteo lytic Activity, C e Tenth	Lipolytic Activity, C e Tenth	Proteo lytic Activity, C e Tenth	Lipolytic Activity, C e Tenth	Proteo lytic Activity, C e Tenth	
		Mg Non coagulable Nitrogen per 100 C e	Mg Non coagulable Sodium per 100 C e	Mg Non coagulable Nitrogen per 100 Gm Dry	Mg Non coagulable Sodium per 100 Gm Dry	Mg Non coagulable Sodium per 100 Gm Dry	
1	Before	37					
	3.5 hours after Alpine lamp, 10 in., 20 min.	30					
	17 hours after first exposure	29					
	4 hours after second exposure	23					
	48 hours after second exposure	24					
	4 hours after third exposure	22					
	72 hours after third exposure	30					
	4 hours after fourth exposure	28					
2	Before	99					
	4 hours after Alpine lamp, 10 in., 20 min.	85					
	72 hours after first exposure	88					
	4 hours after second exposure	80					
	3 weeks after second exposure	100					
	4 hours after third exposure	80					
	48 hours after third exposure	80					
	4 hours after fourth exposure	80					
	1 week after fourth exposure	90					
	4 hours after fifth exposure	72					
3	Before	70					
	4 hours after Alpine lamp, 10 in., 20 min.	62					
	3 weeks after first exposure	65					
	4 hours after second exposure	60					
	48 hours after second exposure	63					
	4 hours after third exposure	63					
	1 week after third exposure	61					
	4 hours after fourth exposure	55					
	24 hours after fourth exposure	60					
	2 hours after fifth exposure (1 hour)	40					
4	Before	49					
	4 hours after Alpine lamp, 10 in., 20 min.	38					
	48 hours after first exposure	31					
	4 hours after second exposure	28					
	1 week after second exposure	36					
	4 hours after third exposure	30					
	24 hours after third exposure	35					
	2 hours after fourth exposure (1 hour)	20					
5	Before	5					
	4 hours after Alpine lamp, 10 in., 20 min.	11					
	24 hours after first exposure	7					
	4 hours after second exposure	5					
6	Before	15					
	1 hour after Alpine lamp, 10 in., 20 min.	6					
	24 hours after first exposure	4					
	4 hours after second exposure	4					
7	Before	6					
	3 hours after Alpine lamp, 10 in., 20 min.	14					
	24 hours after first exposure	12					
	4 hours after second exposure	8					

EFFECT ON LIPOLYTIC FERMENT (LIPASE)

In Table 1, Rabbit 1 showed a titer of 37 before exposure. Seventeen hours after a twenty minute exposure, it was 29; four hours after the second exposure, 23; forty-eight hours after the second exposure, 24;

four hours after the third exposure, 22, seventy-two hours after the third exposure, 30, and four hours after the fourth exposure, 28. There was, therefore, a reduction from 37 to 28 after four exposures.

Rabbit 2 showed a reduction in lipase titer from 99 to 72 after five exposures.

Rabbit 3 after five exposures exhibited a fall from 70 to 40.

Rabbit 4 after four exposures showed a decline from 49 to 20.

Rabbit 9 (Table 2) was sensitized before exposure by an intraperitoneal injection of quinin sulphate. After three exposures, there was a slight decline in the lipase titer from 10.8 to 9.

Rabbit 10 was sensitized by the intraperitoneal injection of eosin. After three exposures, there was a decline from 5.4 to 2.2.

TABLE 2.—Effect of Ultraviolet Light on Blood Serum Enzymes of Rabbits Previously Treated with Photosensitizers

Rab- bit	Treatment	Proteo- lytic Activity, Mg normal Nitrogen per 100 C c	Lipolytic Activity, C c Tenth per 100 C c	Remarks*
8	30 mg eosin per kilogram 30 minutes before exposure to Alpine lamp, 10 inches, 20 minutes	6 24 18 10	1 hour after exposure 24 hours after exposure 4 hours after second exposure	20 mg of quinin sulphate per kilogram, $\frac{1}{2}$ hour before exposure
	1 hour after exposure		8.8	
	24 hours after exposure		10.7	
	4 hours after second exposure		10.6	
9	10 mg quinin sulphate per kilogram 30 minutes before exposure to Alpine lamp, 10 inches, 10 inches, 20 minutes	10.8 8.8 10.7 10.6 10.8 9	1 hour after exposure 48 hours after exposure 1 hour after second exposure 48 hours after second exposure 2 hours after third exposure	20 mg of quinin sulphate per kilogram, $\frac{1}{2}$ hour before exposure 20 mg of quinin sulphate per kilogram, $\frac{1}{2}$ hour before exposure
	1 hour after exposure		8.8	
	48 hours after exposure		10.7	
	1 hour after second exposure		10.6	
	48 hours after second exposure		10.8	
	2 hours after third exposure		9	
10	10 mg eosin per kilogram 30 minutes before exposure to Alpine lamp, 10 inches, 20 minutes	5.4 4.1 4.2 3 3.4 2.2	1 hour after exposure 48 hours after exposure 1 hour after second exposure 48 hours after second exposure 1 hour after third exposure	30 mg of eosin per kilogram $\frac{1}{2}$ hour before exposure 30 mg of eosin per kilogram $\frac{1}{2}$ hour before exposure
	1 hour after exposure		4.1	
	48 hours after exposure		4.2	
	1 hour after second exposure		3	
	48 hours after second exposure		3.4	
	1 hour after third exposure		2.2	

* Both the eosin and quinin sulphate were injected intraperitoneally. In the control animals, neither appeared to modify the enzyme activity.

EFFECT OF ULTRAVIOLET LIGHT ON PROTEOLYTIC FERMENT (PROTEASE) IN BLOOD

Rabbit 5 (Table 1) showed a rise of from 5 to 11 four hours after the first exposure, but a decline to 5 after the second.

Rabbit 6 exhibited a decline in protease from 15 to 4 after two exposures.

Rabbit 7 showed a rise from 6 to 14 after the first exposure and a decline to 8 after the second exposure

Rabbit 8 (Table 2), sensitized with eosin, showed a rise from 6 to 24, and then a decline to 10

In a general way it may be said that ultraviolet light, in the degree that we applied it, appeared to decrease the lipase in the serum of rabbits and to increase the protease. Further, the effects of the exposures seemed temporary, the tendency being for the values to return to their original levels.

EFFECT OF ULTRAVIOLET LIGHT ON THE BLOOD ENZYMES OF HUMAN SUBJECTS

Patient 1 (Table 4) suffering from psoriasis, was exposed to the Alpine lamp (chest and back) for sixteen minutes. A marked reaction (sunburn) developed. The lipase declined from 11 to 7 and the protease from 8 to 6.

Patient 2, suffering from psoriasis, received the same exposures. The lipase declined from 11 to 8, and the protease remained unaltered. Patient 3, suffering from generalized pruritus, was exposed for twenty minutes. The lipase rose from 10.5 to 12.5, and the protease from 8 to 9.

Owing to the paucity of observations on human subjects, no definite deductions can be drawn. In two out of three of the patients, there was a decline in the lipase.

TABLE 3.—Effect of Various Agents (*Turpentine, Vaccines and Neoarsphenamin*) on Blood Serum Enzymes of Rabbits

Rabbit	Treatment	Proteolytic Activity, Mg Non coagulable Nitrogen per 100 C c	Lipolytic Activity C c Tenth Normal Sodium Hydroxid per 100 C c
12	Before		20
	4 hours after intramuscular injection of 5 cc turpentine olive oil emulsion		26
13	Before	3	
	4 hours after intramuscular injection of 5 cc turpentine olive oil emulsion	5	
14	Before		28
	2 hours after subcutaneous injection of staphylococcal vaccine		35
15	Before		30
	4 hours after subcutaneous injection of staphylococcal vaccine		35
16	Before	5	
	4 hours after subcutaneous injection of staphylococcal vaccine	7	
17	Before		40
	2 hours after intravenous injection of neoarsphenamin, 50 mg per kilogram		37
18	Before	4	
	4 hours after intravenous injection of neoarsphenamin, 50 mg per kilogram	3	
	24 hours after injection	4	
19	Before		72
	5 hours after intravenous injection of neoarsphenamin, 50 mg per kilogram		51
	24 hours after injection		59
	72 hours after injection		69

**EFFECT OF INJECTIONS OF TURPENTINE ON THE BLOOD
ENZYMES IN RABBITS AND IN HUMAN BEINGS**

The intramuscular injection of turpentine in 5 c.c. of olive oil into a rabbit was followed, in four hours, by a rise of lipolytic activity from 20 to 26. In another rabbit, the proteolytic activity rose from 3 to 5.

In a patient suffering from eczema, the intramuscular injection of 5 minimis (0.3 c.c.) of rectified turpentine in 5 c.c. of olive oil was followed, in three hours, by a rise of lipolytic activity from 9 to 10, and in proteolytic activity from 8 to 10.

In a case of pemphigus, the same treatment was followed, in three hours, by a rise in lipolytic activity from 10 to 14.5, and in proteolytic activity from 6 to 8.5.

In a case of lupus erythematosus, the injection of turpentine was followed, in three hours, by a rise in lipolytic activity from 9 to 14, and in proteolytic activity from 5 to 7.

It would appear from the foregoing studies that the intramuscular injection of turpentine tends to increase the lipolytic and proteolytic power of the blood serum in both rabbits and human beings.

INFLUENCE OF VACCINES ON BLOOD ENZYMES IN RABBITS

Rabbit 14 received an injection of staphylococcal vaccine subcutaneously. Two hours later, the lipolytic activity of the blood had risen from 28 to 35.

Rabbit 15, treated in the same manner, showed a rise from 30 to 35, at the end of four hours.

Rabbit 16, treated with staphylococcal vaccine, showed, at the end of four hours, a rise in proteolytic activity from 5 to 7. As far as any deduction from these few experiments with vaccines is permitted, it can be stated that a tendency to rise in both lipolytic and proteolytic activity is suggested.

**EFFECT OF INJECTIONS OF NEOARSPHENAMIN ON THE BLOOD
ENZYMES OF RABBITS**

Three rabbits were injected intravenously with neoarsphenamin, 50 mg per kilogram of body weight. This, of course, is a very large dose, equivalent to three grams for a man weighing 60 kg.

In Rabbit 17, the lipolytic activity, after two hours, was reduced from 40 to 37.

Rabbit 18 received 50 mg per kilogram of neoarsphenamin. At the end of four hours, the proteolytic power of the serum was reduced from 4 to 3. Twenty hours later, it rose again to 4.

In Rabbit 19, the lipolytic activity was reduced from 72 to 51 at the end of five hours, rising to 59 after twenty-four hours and to 69 after

TABLE 4.—Effect of Nonspecific Agents on Blood Serum Enzymes of Human Beings

Case	Diagnosis	Treatment	Proteo-	Lipolytic	Remarks
			lytic Activity, C c Tenth	Mg Non- coagulable Nitrogen per 100 C c	
1	Psoriasis	Before			
		4 hours after intramuscular injection of 20 c c autoserum	5	8	
		24 hours after injection	9	19	Mild reaction
		72 hours after injection	7	17	
2	Pruritus	4 hours after second injection	6	15	
		Before		21	
		4 hours after intramuscular injection of 20 c c autoserum		8	
3	Pruritus	Before	7	9	
		25 hours after intramuscular injection of 20 c c autoserum	12	11	
4	Psoriasis	Before		7	
		3 hours after intramuscular injection of 20 c c autoserum		12	
6	Eczema	Before	8	9	
		3 hours after intramuscular injection of 5 m turpentine in olive oil	10	10	
7	Pemphigus	Before	6	10	
		3 hours after intramuscular injection of 5 m turpentine in olive oil	8.5	14.5	
9	Psoriasis	Before	8	11	
		2 hours after Alpine lamp, 16 minutes exposure back and front	8	8	Marked cutaneous reaction
10	Psoriasis	Before	8	11	
		2 hours after Alpine lamp, 15 minutes exposure back and front	8	8	Marked cutaneous reaction
5	Psoriasis	Before	10	7	Temperature, 100 F, chills
		4.5 hours after intramuscular injection of 20 c c autoserum	17	8	
		10 days after injection	7	8	
		6 hours after second injection serum	5	8	
13	Psoriasis	Before	12	6.5	
		3 hours after intravenous injection of 1.5 c c distilled water	10	6.5	
11	Acne	Before	10	8	
		2 hours after Alpine lamp exposure for 10 minutes	11	8	Treatment applied to face
12	Pruritus	Before	8	10.5	
		2 hours after Alpine lamp exposure for 20 minutes	9	12.5	Cutaneous reaction
8	Lupus erythematosis	Before	5	9	
		3 hours after intravenous injection of 5 m turpentine in olive oil	7	14	
14	Normal	Before	15	11	
		2 hours after intravenous injection of 1.5 c c distilled water	8	6	
		6 days after injection	12	8	
		25 hours after second injection	8	6	Reaction

seventy-two hours. It would appear that, in rabbits, large doses of neoarsphenamin tend to depress the lipolytic and proteolytic activity of the blood serum.

THE EFFECT OF INTRAMUSCULAR AUTOBLOOD INJECTIONS IN HUMAN BEINGS ON THE SERUM ENZYMES

A patient with psoriasis had 20 c c of blood withdrawn from a vein and immediately injected into the gluteal muscles. Before the injection, the lipolytic activity of the blood serum was 8. Four hours later, it was

19, twenty-four hours after the injection, it was 17, declining to 15 after seventy-two hours. Four hours after a second injection, at the end of seventy-two hours, it rose to 21.

The proteolytic activity rose from 5 to 9 after four hours, declining to 7 at the end of twenty-four hours, and to 6 at the end of seventy-two hours.

Patient 2, with generalized pruritus, treated with autoblood in the same manner as the preceding case, showed a rise in lipolytic activity at the end of four hours from 8 to 14.

Patient 3, suffering from generalized pruritus, received an autoblood injection and at the end of two and a half hours exhibited a rise in lipolytic activity of his blood serum from 9 to 11, and in proteolytic activity from 7 to 12.

Patient 4 (psoriasis), treated with autoblood injection, showed a rise of lipolytic activity from 7 to 12 at the end of three hours.

Patient 5 (psoriasis) showed a rise in lipolytic activity from 7 to 8. The proteolytic activity rose after four and a half hours from 10 to 17; ten days later, it was 7. Six hours after a second (intravenous) injection of 13 c.c. of autoserum, it was 5.

EFFECT OF ULTRAVIOLET LIGHT ON THE LIPOLYTIC AND PROTEOLYTIC ENZYMES OF THE SKIN IN RABBITS

As the skin of treated rabbits could be tested by the method employed by us only after death of the animal, an effort was made to determine the average normal enzyme activities in untreated control animals. The skin of four untreated rabbits showed a lipolytic activity varying from 80 to 100 c.c. of tenth normal sodium hydroxide per hundred grams of dry skin, and a proteolytic activity varying from 6,000 to 8,000 mg per hundred grams of dry skin.

Rabbit 2, after five exposures to ultraviolet light, showed a titer of 5,500 for proteolytic activity, and 98 for lipolytic activity.

Rabbit 3, after four exposures to ultraviolet light, showed a titer of 4,000 for proteolytic activity, and 70 for lipolytic activity.

Rabbit 4, after four exposures, showed a titer of 3,500 for proteolytic activity, and 50 for lipolytic activity.

The foregoing studies would seem to warrant the conclusion that exposure to ultraviolet light depresses the proteolytic and the lipolytic activity of the skin of rabbits, the former being influenced more than the latter.

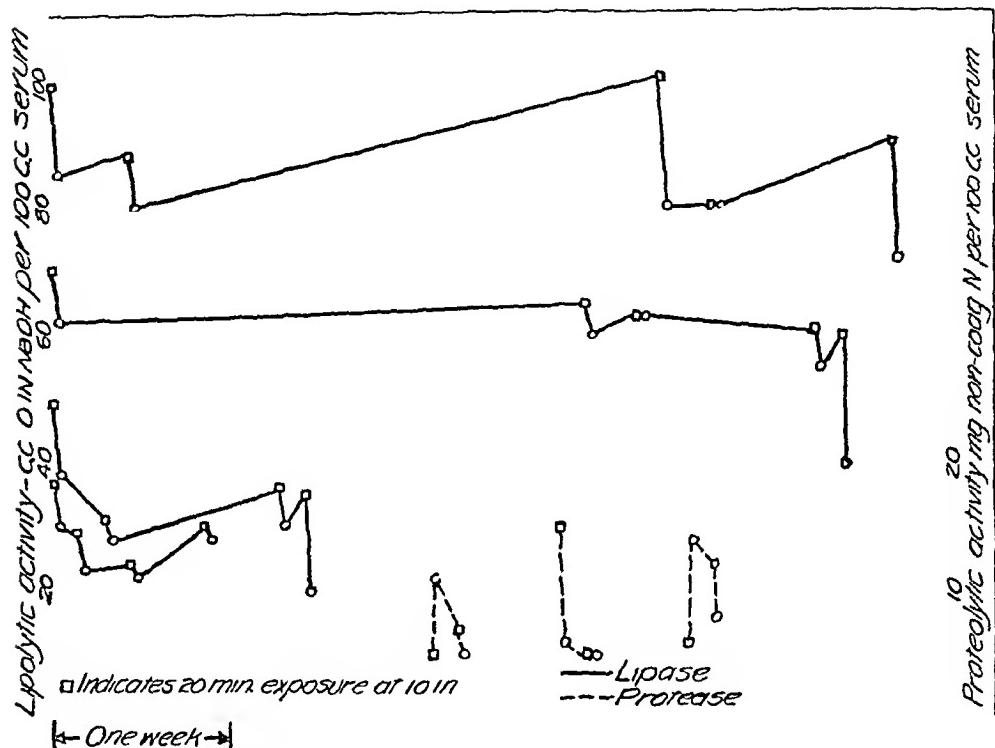
Since the normal lipolytic values of the blood in our rabbits appear to be subject to wide individual variations, the same may be true of the rabbit skin. The figures submitted, therefore, in the determinations of enzyme activity in the four normal rabbit skins are given with reservation.

EFFECT OF INTRAVENOUS INJECTION OF DISTILLED WATER

A patient suffering from muscular pains was given 15 cc of distilled water intravenously

Before the injection, the lipolytic activity was 11, two hours later, it declined to 6, six days later, it was 8. Two and a half hours after a second injection, it declined again to 6.

The proteolytic activity before the injection was 15. After two hours, it declined to 8, at the end of six days, it was 12. Two and a half hours after a second injection, it was reduced to 8.



form. The tube was shaken sharply until a milky emulsion was formed. A control tube containing 1 cc of serum was heated on the water bath for thirty minutes at 60°C, after which 0.5 cc of toluene was added. Both tubes were stoppered with cotton and incubated for 48 hours at 37°C. From time to time, the chloroform tube was shaken to maintain the emulsion. Two cubic centimeters of water was then added to each tube, and 1 cc of a 20 per cent solution of sodium chloride in 10 per cent acetic acid. Both tubes were then warmed to remove the chloroform and toluene and placed in boiling water for ten minutes. The tubes were then cooled, diluted to 10 cc, filtered, and the nitrogen determined on 5 cc of the titrate by the usual micromethod. The difference in the nitrogen values, calculated to 100 cc of serum, is a measure of the proteolytic activity of the serum.

Serum Lipase.—One cubic centimeter of blood serum, 1 cc of neutral (phenolsulphonephthalein) ethylbutyrate, 1 cc of toluene and 7 cc of 0.85 per cent salt solution were placed in a 100 cc Erlenmeyer flask. To another flask were added 1 cc of ethylbutyrate, 1 cc of toluene and 8 cc of 0.85 per cent salt solution. To a third flask were added 1 cc of blood serum, 1 cc of toluene and 8 cc of 0.85 per cent salt solution. Each flask was shaken 100 times, stoppered with cotton and incubated at 37°C for four hours. The flasks were then placed in ice water, 15 cc of neutral alcohol and 4 drops of a 1 per cent alcoholic solution of phenolsulphonephthalein added to each and then titrated rapidly with tenth normal sodium hydroxide. The titer, corrected for the blanks, when calculated to tenth normal per hundred cubic centimeters, was taken as a measure of the lipolytic or esterase activity.

The skin enzymes were determined according to the methods of Sexsmith and Petersen² except that a 1 per cent skin suspension was used.

The proteolytic activity was determined by starting with an initial p_H of 5.5. For the autolysis, however, the initial reaction of the suspension was not altered.

A search of the literature reveals very sparse data bearing directly on the studies here reported.

Wells³ says:

In view of the fact that enzymes and antibodies in solution are quite readily weakened or destroyed by the action of light, it is possible that intracellular enzymes may be similarly destroyed by light, with resulting cell death.

² Sexsmith, E., and Petersen, W. J. Exper. Med. **27**, 273, 1918.

³ Wells, H. G. Chemical Pathology, Ed. 3, Philadelphia, W. B. Saunders Company, 1918, p. 374.

Bering⁴ found that chemically active light rays have a direct action on oxidizing enzymes

Burge, Fischer and Neill⁵ state that hormones, proenzymes and enzymes are destroyed by exposure to ultraviolet radiation. The rate of destruction is proportional to the amount of energy applied. (Experiments were performed *in vitro*, the enzyme solutions being subjected to long exposures, from one to three hours, and then tried out for activity on definite substrates.)

Jobling and Petersen⁶ conclude that the serum ferments are practically unaltered by a primary injection of a foreign protein. Acute

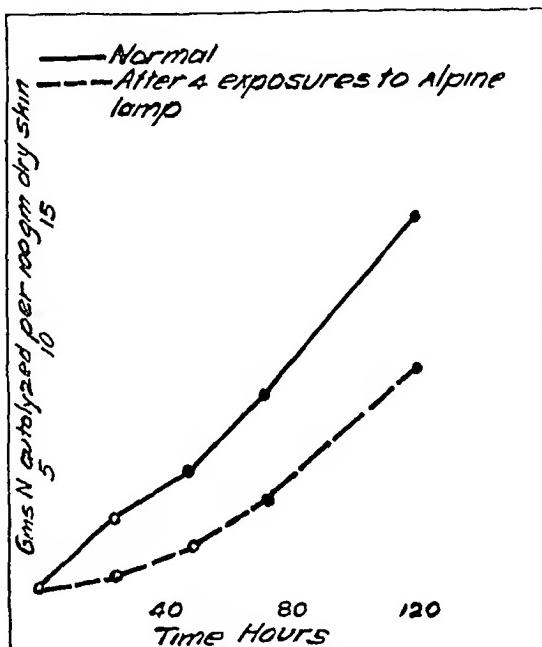


Chart 2—Comparative autolysis of normal rabbit skin and that of rabbit exposed to ultraviolet light

shock produces an instantaneous increase in protease, followed later by an increase in serum lipase. They state that the shock is produced by the protease splitting various proteins down to the toxic peptone stage.

Jobling, Petersen and Eggstein⁷ found that the intravenous injection of killed organisms is followed by the mobilization of nonspecific protease and lipase, the rapidity and extent of this reaction depend on the toxicity of the organism and on its resistance to proteolysis. The temperature and leukocyte curve bear no relation to the ferment changes.

4 Bering Munchen med Wchnschr **59** 2975, 1912

5 Burge, W E, Fischer, W R, and Neill, A J Am J Physiol **40** 425 (May) 1916

6 Jobling and Petersen J Exper Med **22** 401, 1915

7 Jobling, Petersen and Eggstein J Exper Med **22** 603, 1915

Pincussen and Anagnostin⁸ studied the effect of roentgen rays and nitra-lamp radiation on the serum lipase. The results, in general, showed that radiation of either the serum or the animal from which the serum was taken reduced the lipase activity. On the other hand, diathermy, as well as galvanism, when applied to the living animal, led to a significant increase.

It has been found that ferments lose their power under strong exposure to light⁹. Ferments may be destroyed by exposure to the visible as well as to the ultraviolet end of the spectrum. Green¹⁰ found that amylase is destroyed by short wave length rays. On the other hand, the visible rays activate this enzyme through influence on the zymogen.

Chymosin, katalase and peroxidase, which are but slightly injured by exposure to the visible rays, are readily and permanently made inert by exposure to the short wave rays. The action of long wave rays on enzymes was first described by Downes and Blunt, the discoverers of the bactericidal action of light.

Bering and Meyer¹¹ demonstrated that peroxidase, exposed to light, acquired an increased activity. This was more particularly true of the short wave lengths.

It will be seen from the foregoing references that all these experiments were carried out *in vitro*.

That intracellular ferments may be influenced by light *intra vitam* was shown by the careful researches of Ostwald¹² on the peroxidase and katalase content of different heliotropic animals. The katalase content of living "raupchen" of *porthesia chrysorrhea* is strikingly lessened by exposure to light. The physiologic production of katalase is apparently favored by green light, but restricted by violet light. The production of peroxidase is stimulated to the same extent that katalase is destroyed.

Pincussen¹³ believes that all cells possess their own ferments, which may be thrown into the blood when the cells break up. He states that exposure to light stimulates this.

CONCLUSIONS

1 Ultraviolet light, in the strengths used by us from an Alpine lamp, appears to decrease the lipolytic activity of the blood serum both

8 Pincussen and Anagnostin Biochem Ztschr **128** 268, 1922

9 Hausmann Grundzuge der Licht-biologie und Pathologie, Berlin, Urban and Schwarzenburg, 1923

10 Green, quoted by Euler Chemie der Enzyme, Munchen-Wiesbaden, 1920, p 197

11 Bering and Meyer Strahlen-therapie, **1** 411, 1912

12 Ostwald Biochem Ztschr **10** 1, 1908

13 Pincussen, quoted by Hausmann (Footnote 9, p 30)

in rabbits and in human beings. On the other hand, the proteolytic activity of the blood serum appears to be increased.

2 The intramuscular injection of therapeutic doses of turpentine in olive oil tends to increase the lipolytic and the proteolytic power of the blood serum both in rabbits and in human beings.

3 Limited observations on the effect of subcutaneous injections of staphylococcal vaccines suggest that they tend to increase both the lipolytic and proteolytic activity of the blood serum.

4 The intramuscular injection of freshly drawn autoblood appears to stimulate an increase in the lipolytic and proteolytic activity of the blood serum.

5 The injection of large doses of neoarsphenamin in rabbits (equivalent to 3 gm for a man weighing 60 kg) tends to depress the lipolytic and proteolytic activity of the blood.

6 Observations on two cases suggest that the intravenous injection of small quantities (15 c.c.) of distilled water tends to decrease the lipolytic activity of the blood and perhaps the proteolytic power.

7 The exposure of rabbits to ultraviolet light from an Alpine lamp decreases the lipase and the protease in the skin of an animal.

8 In summarizing, it may be said that injections of vaccines, turpentine and autoblood appear to increase the lipase and protease in the blood, while huge doses of neoarsphenamin and small doses of distilled water tend to decrease them. Ultraviolet light depresses the lipase, and stimulates the protease.

PATHOLOGIC CHANGES OCCURRING IN WHITE
RATS RAISED ON DIETS DEFICIENT IN
VITAMIN A^{*}

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It now seems well established that there are two distinct factors concerned in the Fat-Soluble A vitamin. One is antirachitic. The other is antixerophthalmic and growth promoting, and retains the appellation vitamin A.

The bony lesions following a dietary regimen in which the antirachitic factor has been lacking have been described.¹ Among other lesions resulting from this deficiency, Kauffman, Creekmur and Schultz² have described changes in the middle ear resulting in varying degrees of deafness. Grieves³ also claims that dental caries is another manifestation of the upset in calcium metabolism.⁴ There has also been mentioned in connection with rickets of a certain type an upset in nervous equilibrium due to an improper calcium balance,¹ while Reynolds and Macomber⁵ assign to the same cause some cases of sterility.

The absence of vitamin A from an otherwise adequate diet will cause a cessation of growth soon followed by the characteristic eye lesions so well described by Mori.⁶ He also showed that the salivary glands undergo a cessation of secretory activity analogous to that undergone by those of the orbit. Daniels, Armstrong and Hutton⁷ have recently emphasized the fact that the lack of vitamin A is the specific

* From the department of physiology, University of Oregon Medical School
1 Shipley, P G , Park, E A , McCollum, E V , and Simmons, Nina Is There More Than One Kind of Rickets? Am J Dis Child **23** 91-106 (Feb) 1922

2 Kauffman, A B , Creekmur, Francis, and Schultz, O T Changes in the Temporal Bone in Experimental Rickets, J A M A **80** 681-685 (March 10) 1923

3 Grieves, C J The Effect of Defective Diets on Teeth, J A M A **79** 1567-1573 (Nov 4) 1922

4 We have noted in our own work a greatly increased fragility of the teeth of deficient rats, and, in some instances, we have found a stub where a brittle tooth had snapped off.

5 Reynolds, Edward, and Macomber, Donald Defective Diet as a Cause of Sterility, J A M A **77** 169-175 (July 16) 1921

6 Mori, S Changes in Para-Ocular Glands Which Follow Administration of Diets Low in Fat-Soluble A, Effect of Same Diets on Salivary Glands and Mucosa of Larynx and Trachea, Bull Johns Hopkins Hosp **33** 357-359 (Oct) 1922

7 Daniels, Amy L , Armstrong, Margaret E , and Hutton, Mary K Nasal Sinusitis Produced by Diets Deficient in Fat-Soluble A Vitamin, J A M A **81** 828-829 (Sept 8) 1923

factor that permits another disorder to develop which they have termed paranasal and mastoid sinusitis. Because of this deficiency, bacterial invasion of the mucous membranes of the ear and nasal cavities is made possible.

The results of experiments with vitamin A deficient diets seem to justify two general statements: first, that cellular activity is minimized, and second, that out of this reduction in activity comes an increased susceptibility to infections hastening the termination of the experiment. A finer analysis of the first of the preceding statements will show that the results of a lessened cellular activity will depend on the type of cell affected. If there is a curtailment of the activity of somatic cells, the first result will be failure to produce new cells—stoppage of growth, the second, inability to replace cells already existing—loss of maintenance, and the third, actual regression. If there is a diminution in the activity of glandular cells, the results will vary with the type of gland affected and, in general, there will be a lessened resistance to infection, malnutrition and sterility.

Vitamin A is a substance necessary for the normal functioning of the body tissues. It is not clear just how it meets this necessity. It may either be one of the essential ingredients needed in cell structure or it may act as a hormone making available some necessary component in cell formation. In either case, it is absolutely essential for the cell multiplication necessary for growth and maintenance.

In general, growth is proportional to the supply of vitamin A. Normally, a rat matures at three months of age. It also obtains about three fourths of its body weight in that time. At the very time in a rat's life when the bulk of the vitamin A supply is no longer needed for growth, the reproductive organs begin to function. Most of the vitamin A intake during the first three months of a rat's life is used for the formation of new cells throughout the body. When the animal has practically attained its growth and the majority of the new somatic cells needed are those required for replacement, the vitamin A supply is utilized in new quarters, in the glandular elements, where cell increase suddenly takes a tremendous impetus, which it maintains throughout the vigorous span of a rat's life. The rat is now mature, the sexual function is established, and the nervous, respiratory and digestive systems have become stabilized by proper and sufficient glandular activity.

The purpose of this paper will be to offer observations in support of the preceding statements, and to show that a vitamin A deficiency causes such a reduction in cellular activity as to amount to a pluriglandular deficiency, and that this in turn brings about secondary changes directly leading to death.

The technic of the feeding experiments conforms as closely as possible to the rules governing such experimentation. A description of methods has appeared so many times in the literature that, aside from saying no departures were made from the best approved methods, nothing further will be added.

Our work confirms in many respects the findings mentioned above, and brings out additional pathology of this deficiency. For some time, we have observed that our rats on a vitamin A low diet, when reaching a stationary nutritive regimen, could be made to do much better by the simple expedient of moistening their food. The food is ordinarily in a semidry, caked condition. For the first seven or eight weeks, they eat enough of the food in this condition to produce fair growth curves. Then ensues a period of variable length, from one to three weeks, when they either become fussy and scatter the food about the cage or act indifferently toward it. If sufficient moisture is now added to the food, this condition does not become so acute. As implied above, we are inclined to attribute this to the xerostomia and to consider it an early sign of the specific vitamin deficiency. This dry condition of the mouth is further demonstrated in the following manner. Several small cotton swabs of uniform size and firmness are made. They are slightly moistened in a solution of brom thymol blue, which will turn blue when in contact with the alkaline saliva. One swab is used for each rat. An equal number of normal rats are similarly treated for controls. The moistened applicator is placed in the rat's mouth and thoroughly swabbed about. In the normal animals, the cotton immediately takes on a very dense blue color, while with the test animals the color appears fainter in hue and occurs in spots and patches, indicating a lessened amount of salivary secretion.

With the procedure just described, a fairly accurate estimate may be obtained of the hydrogen ion concentration of the saliva, of the secretions of the vagina and the rectum, of the peritoneal fluid and of the blood serum. In such instances, the swabs were matched for color to a series of swabs made from buffer solutions of known hydrogen ion concentration. Thus it was that we found that the reaction in the mouth of a rat suffering from xerophthalmia and xerostomia had changed from the normal alkaline condition of p_H 7.4 to an acid one of p_H 6.6. This was due to a decrease in the alkaline saliva, increased stasis of intra-oral material and bacterial activity.

This condition of dryness does not exist in the mouth alone. Mori⁶ found it in the eyes. We have found that it involved the upper part at least of the trachea, for such rats, when given painful stimuli, are unable to squeal as do normal rats when similarly stimulated, but give forth, instead, a dry, husky cry or none at all, depending on the degree of

involvement. This attempt at a cry is accompanied by the usual facial grimaces, and is undoubtedly an attempt on the part of the rat to give voice to his discomfort. This dysarthria is additional evidence of the general xerosis due to glandular insufficiency, and is analogous to a similar condition, described by Mori,⁶ occurring in school children suffering with xerophthalmia.

This lack of glandular activity does not seem to be limited to the para-ocular, paranasal and para-oral glands. The dryness of the feces and of swabs applied to the rectum, large bowel and vagina seems to indicate that here, too, is a lessening in the secretions. There are still other evidences of vitamin A deficiency that can very well be associated with the lack of glandular activity noted in the foregoing. These are the lack of gonadal activity as manifested by variations in reproductive ability, marked underdevelopment of the seminal vesicles, lessening of the mammary secretion, due both to incomplete development and to decreased function, and a curtailment in the secretory activity of the oil glands of the skin, resulting in a dry, blistering hair, which falls out much more readily than that of normal animals. More could be said concerning the changes occurring in the reproductive system, but this material is being reserved for a future report.

The marked decrease in cellular activity noted above should be considered the primary pathologic change resulting from vitamin A deficiency. The decrease in secretions promotes desquamative changes, destroys the action of cilia, lowers bactericidal ability, and, in many other ways, provides portals for entry of numerous organisms that soon produce pyogenic lesions with their associated complications. These should be considered as secondary pathologic changes resulting from a lack or shortage in vitamin A.

Our necropsy records of such deficient rats show that a large majority of them had pyogenic infections. In many instances, we found the posterior third of the tongue the seat of abscesses ranging in severity from a single small centrally placed abscess to an involvement in which there was almost total destruction of that portion of the tongue. The organisms causing these central abscesses seemed to have gained entrance either through the foramen cecum or that tissue representing its vestiges. Other abscesses, more laterally placed and generally much more extensive and destructive, had their origin from material escaping from the ruptured salivary ducts leading from the submaxillary and sublingual glands. In all cases of lingual abscesses, the sublingual and submaxillary glands were found infected, their ducts greatly distended with purulent material and the region of their opening beneath the tongue always marked by cystic dilatation. Other abscesses have been found on the borders of the lips. These oral abscesses must be of prime importance.

involvement. This attempt at a cry is accompanied by the usual facial grimaces, and is undoubtedly an attempt on the part of the rat to give voice to his discomfort. This dysarthria is additional evidence of the general xerosis due to glandular insufficiency, and is analogous to a similar condition, described by Mori,⁶ occurring in school children suffering with xerophthalmia.

This lack of glandular activity does not seem to be limited to the para-ocular, paranasal and para-oral glands. The dryness of the feces and of swabs applied to the rectum, large bowel and vagina seems to indicate that here, too, is a lessening in the secretions. There are still other evidences of vitamin A deficiency that can very well be associated with the lack of glandular activity noted in the foregoing. These are the lack of gonadal activity as manifested by variations in reproductive ability, marked underdevelopment of the seminal vesicles, lessening of the mammary secretion, due both to incomplete development and to decreased function, and a curtailment in the secretory activity of the oil glands of the skin, resulting in a dry, bristling hair, which falls out much more readily than that of normal animals. More could be said concerning the changes occurring in the reproductive system, but this material is being reserved for a future report.

The marked decrease in cellular activity noted above should be considered the primary pathologic change resulting from vitamin A deficiency. The decrease in secretions promotes desquamative changes, destroys the action of cilia, lowers bactericidal ability, and, in many other ways, provides portals for entry of numerous organisms that soon produce pyogenic lesions with their associated complications. These should be considered as secondary pathologic changes resulting from a lack or shortage in vitamin A.

Our necropsy records of such deficient rats show that a large majority of them had pyogenic infections. In many instances, we found the posterior third of the tongue the seat of abscesses ranging in severity from a single small centrally placed abscess to an involvement in which there was almost total destruction of that portion of the tongue. The organisms causing these central abscesses seemed to have gained entrance either through the foramen cecum or that tissue representing its vestiges. Other abscesses, more laterally placed and generally much more extensive and destructive, had their origin from material escaping from the ruptured salivary ducts leading from the submaxillary and sublingual glands. In all cases of lingual abscesses, the sublingual and submaxillary glands were found infected, their ducts greatly distended with purulent material and the region of their opening beneath the tongue always marked by cystic dilatation. Other abscesses have been found on the borders of the lips. These oral abscesses must be of prime importance.

as reasons for the rats' refusal to eat, and undoubtedly share in the explanation of their nutritive decline⁸

In most cases, mucopurulent material has been found in the nasal sinuses and middle ear due to direct extension from the nasal tracts and eustachian ducts Large purulent plugs have been found in the nasopharynx which had their origin as drainage from the higher respiratory areas These plugs frequently acted as a serious menace to free respiration In these particular instances, the rats would have paroxysmal spells of sneezing, which would produce marked cyanosis and pronounced exhaustion It is likely that during these paroxysms particles became dislodged and were aspirated further into the respiratory tract, producing numerous purulent deposits in the lungs Necropsies on such animals seemed to indicate such a course Thus, the infection was spread to the pulmonary tissues, and extensive empyemic areas developed We have seen numerous cases in which the lung tissue was almost entirely replaced by immense accumulations of pus These animals did not seem to die so much from the infection itself as from the gradual obliteration of the respiratory tissue and the resultant asphyxia Respirations would become more dyspneic, and oxygenation so poorly accomplished that the rat would have to minimize all physical effort Even then he would gradually become more cyanosed, lose

8 I was an interested witness at a necropsy recently held at the Multnomah County Hospital The body examined was that of a Chinese, aged 55 He was 5 feet 9 inches (175.2 cm) in height, and weighed 100 pounds (45.4 kg) His body was very emaciated No clinical diagnosis had been made, as he persistently refused to answer all questions, stating over and over again that he was all right Physical examination was negative, except for small enlargements on both sides of the throat in the region of the submaxillary glands The teeth were extremely bad The urine was negative, except for a trace of albumin and a few casts The history, so far as obtained, was also negative He was in the hospital only a few days before he died, and during that time steadily refused all food, drink and medication Toward the last, he even refused to have his temperature taken by mouth He talked very little, and then only by urging The temperature averaged 97 F, running at times as low as 94 and as high as 98.2 The pulse was 80, and the respirations 20 The only complaint was a "burning in the throat" He rapidly grew weak, and toward the last was occasionally irrational Outside the usual senile changes and evidences of arteriosclerosis, the necropsy findings were negative, except for these very significant points A large abscess beneath the tongue was found at the point of exit of the submaxillary ducts, the ducts themselves were distended with pus and the glands were greatly enlarged and engorged with purulent material, the esophagus presented numerous submucous abscesses, and the posterior portions of the lungs were congested Although the cause of death was given as hypostatic pneumonia, it is evident that this is only a partial truth and does not explain the primary condition leading to this result It is difficult to understand how a human being living in the midst of our modern life could die from a deficiency such as described above, yet it must be considered a possibility Especially is this true when one considers how near to the border of adequacy are many of the menus of an average person's diet

steadily in body heat, and, finally, die of exhaustion and malnutrition and the associated low grade intoxication

By direct extension from the nasopharynx, the infection spread to and involved the middle ear, and, in some cases, became so severe in this location that the vestibular apparatus also became involved, causing the animal to show circus movements. Frequently, the stomach is found containing purulent material which has been swallowed from the nasopharynx. Small abscesses have been found on the borders of the eyelids, others at the bases of the nails, and, in one case, a large pus pocket was found embedded in the wall of the vas

In regard to the multiple purulent onychia noted above, it should be mentioned that Haden and Jordan⁹ have reported experimental work in which they claim that multiple onychia can be produced as a result of a blood borne infection having as a source septic foci in the teeth. Grieves⁸ has found that such infective foci exist as a result of these defective diets. It would therefore seem probable that this case of multiple purulent onychia is an exceptional graphic demonstration of the generalized infection that affects many of these deficient rats.

Mention has been made elsewhere in the literature of the fact that normal rats, under laboratory conditions, occasionally develop a peculiar infection of the lungs that causes death. This condition is similar to that described above but is in less aggravated form and only occurs (a) in old rats, (b) in those which have been subjected to too heavy a reproductive strain and, as a result, have their resistance lowered to a critical point, and (c) in those whose vitality was never on a par with that of their mates. Any change from the normal habitus of an animal will make it more susceptible to the inroads of disease, and, for that reason, only the most robust and vigorous should be selected for experimental purposes. It must not be forgotten that the same tendencies are inherent in vigorous animals, and that it takes only some additional load, such as a defective diet, to make the same diseases appear in them.

It will thus be seen how the decrease in the secretory elements of the eyes and mouth lowers the resistance to invading organisms which soon dominate the situation with serious results. Histologic sections of the trachea reveal a desquamated and eroded condition. In the lungs, the alveoli can be seen breaking down to form larger cavities. Wherever the lining of the alveoli is eroded or broken through, numerous organisms can be seen invading the surrounding tissue. This infection cannot be of pronounced virulence, for occasionally normal animals develop the snuffles and recover with no further extension of the infection. The

⁹ Haden, R. L., and Jordan, W. H. Multiple Onychia as a Manifestation of Focal Infection, *Arch Dermat & Syph* 8:31-36 (July) 1923.

test rats become affected in the same degree as their diet is deficient. If the diet is only moderately deficient or if the animal is of greater vigor, the infection is overcome but recurs again and again with increasing severity as the deficiency becomes more and more pronounced.

The lung condition above described is decidedly at variance with another pulmonary involvement which also occurs but in which the pyogenic agency does not play so prominent a part. Rats dying of the latter condition do not run so long a course. The process is more fulminating and is not always associated with a metabolic decline, that is, their growth curves may still be on the ascent. They will, nevertheless, generally show slight pyogenic involvement at the base of the tongue or in the ears. The nose, however, instead of containing mucopurulent material, has a serosanguineous exudate which discharges quite freely from the nares. The tracheal mucosa is inflamed and covered with a sanguineous exudate. The lungs are extremely congested. This is evidently a bronchogenic pneumonia of a sufficiently virulent type to overwhelm the animal before much loss in body weight has occurred.

The fatalities resulting from the infections described in the foregoing are not due, according to Werkman,¹⁰ to any reduction in the cataphylactic activity of the animal. Findlay¹¹ showed that in vitamin B deficient pigeons, the resultant loss in body heat was the decisive factor in the development of fatal pneumonias. In our animals, loss of heat could not have been a factor since their temperatures did not decline from the normal 101 to 102 F for many days after the infection was obviously present. In fact, a drop in temperature was almost always associated with a slowing of the respiratory rate and the two together considered as early signs of death. We have frequently observed rats with a body temperature so low as not to be obtainable with an ordinary clinical thermometer and with respiratory rates of 16 to 20 a minute. Any influence of a possible resultant thrombopenia on susceptibility to infection cannot be claimed as the evidence is too conflicting.¹²

COMMENT AND SUMMARY

In general, the results of test feeding depend to a great extent on the time in a rat's life when the experimental dietary is commenced. We

10 Werkman, C H. Immunologic Significance of Vitamins, Influence of Lack of Vitamins on Production of Specific Agglutinins, Precipitins, Hemolysins and Bacteriolysins in Rat, Rabbit and Pigeon, *J Infect Dis* **32** 247-254 (April) 1923.

11 Findlay, G M. B Vitamin and Pneumococcal Infection, *Lancet* **1** 714-715 (April 8) 1922.

12 Cramer, W., Drew, A H., and Mottram, J C. Behavior of Platelets in Vitamin A Deficiency and Technique of Counting Them, *Brit J Exper Path* **4** 37-44 (April) 1923. Bedson, S P., and Zilva, S S. Influence of Vitamin A on Blood Platelets of Rat, *Brit J Exper Path* **4** 5-12 (Feb.) 1923.

wish to emphasize the fact that on this point depends whether or not the results noted are due to functional or to organic changes. If a rat is used for experimental feeding tests after it has attained its growth, the results will be more or less due to functional disturbances, while those obtained with rats that are fed test diets during the growing stage will be due to organic changes. Especially is this true of vitamin A underfeeding. A rat raised on a diet lacking only in vitamin A has a pluriglandular deficiency in substance as well as in secretion such that normality cannot be established by any increase in the vitamin A fraction. The best that could be expected on an optimal diet would be a maximum efficiency for what tissue it possesses. On the other hand, adult rats whose tissues have matured but are in a nonfunctioning condition because of the lack of these essential elements, can be restored to their original activity when the missing factors are supplied.

Stress is laid on the point that not only must a diet be adequate in all respects but that it must also be presented to the body at a time when its life's forces can utilize it in the formation as well as the operation of its cellular units.

The pathologic condition arising from vitamin A deficient diets has been described under two heads, primary and secondary. The primary change occurring is a generalized decrease in glandular activity resulting in xerosis of the eye, mouth, larynx and skin, and in malnutrition and sterility. This makes possible the secondary changes that occur, namely, those produced in the eye, nose, mouth and lungs by bacterial invasion.

THE RESPIRATORY ORGANS IN HEALTH AND IN DISEASE

XVIII THE VITAL CAPACITY OF THE LUNGS IN CHRONIC FIBROUS
PLEURISY, HEALED EMPYEMA AND PULMONARY TUBERCULOSIS
BOTH CLINICAL AND NONCLINICAL¹

J A MYERS, MD

AND

C H RICE, BS

MINNEAPOLIS

In an earlier study it was stated that "groups of cases with evidence of parenchymatous lesions showed reduction in the average vital capacity. The average vital capacity was found to decrease with the extent of disease revealed by the roentgen-ray and physical signs. There was also a decrease in the average vital capacity with increase of symptoms." Since that time, considerable new data have accrued. As the data are treated somewhat differently in this study, we felt that it would be permissible to include some of those used in the earlier study. The vital capacity percentages were taken from tables¹ prepared from Dreyer's² weight formulas and West's³ surface area method.

When 773 cases were grouped according to physical signs, 338 were found to be negative. This group of negative cases presented an average vital capacity of 102.4 per cent of the theoretical normal. The average percentage of vital capacity previously reported⁴ in 149 cases was 103.6 per cent of the normal. These figures agree quite closely with those reported by others for persons ranging in age from 18 to 40 years. Most

* Presented before the medical staffs of the Lymanhurst School for Tuberculous Children and the Parkview Sanatorium, June 24, 1924.

¹ From the department of internal medicine and the department of preventive medicine and public health, University of Minnesota Medical School, and the Parkview Sanatorium.

² This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

1 Myers, J A Studies on the Respiration Organs in Health and Disease, VIII, A Method for Quickly Obtaining the Percentage of an Individual Theoretical Normal Vital Capacity of the Lungs, Am Rev Tuberc 7 161 (May) 1923

2 Dreyer, Georges Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet 2 227 (Aug 9) 1919 Dreyer, Georges, and Hanson, G F The Assessment of Physical Fitness, New York, Paul B Hoeber, 1921

3 West, H F Clinical Studies on the Respiration, VI, A Comparison of the Various Standards for the Normal Capacity of the Lungs, Arch Int Med 25 306 (March) 1920

4 Myers, J A Studies on the Respiration Organs in Health and Disease, VII, A Correlation of Symptoms, Vital Capacity Readings and Physical and X-Ray Findings in 619 Cases Examined for Pulmonary Tuberculosis, Am Rev Tuberc 6 702 (Oct) 1922

of the cases presented in this study are within these age limits. In forty-seven of our cases, the diagnosis was reserved on first examination because the evidence was not sufficient to justify either a positive or a negative diagnosis. In Table 1, it will be seen that the average vital capacity for this group was 98.7 per cent of the theoretical normal. When physical signs are present to justify a classification of minimal tuberculosis, ninety-eight cases with symptoms A present an average vital capacity of 90 per cent, thirty-two cases with symptoms B present an average vital capacity of 81.3 per cent, while six cases with symptoms C present an average vital capacity of 77.4 per cent, of the theoretical normal.

Table 1 shows that when the physical signs justify diagnosis of moderately advanced and far advanced disease, the vital capacity is very materially decreased and the decrease becomes more marked with increase in symptoms.

TABLE 1.—Seven Hundred and Seventy-Three Cases Grouped According to Symptoms and Physical Signs

	Number of Cases	Average Vital Capacity
Negative Diagnosis reserved	338	102.4
Pulmonary tuberculosis	47	98.7
Minimal A	98	90.0
B	32	81.3
C	6	77.4
Moderately advanced A	68	83.0
B	66	74.1
C	11	69.5
Far advanced A	34	53.0
B	52	50.7
C	21	42.6
Total	773	

In Table 2, 717 cases are grouped according to roentgen-ray findings. In 112 of these cases in which the stereoscopic plates revealed no evidence of disease, the average vital capacity was found to be 104.1 per cent of the normal. When chronic fibrous pleurisy is present, it will be seen that the average vital capacity is approximately 10 per cent lower than in the normal cases. A slightly greater reduction was found in twenty-six cases with healed empyema.

When lesions were revealed in the lung parenchyma, we did not possess a method of determining accurately the volume of lung tissue involved, therefore, the cases were grouped according to an estimated volume of involvement. Those with shadows "above the first rib" (Table 2) did not all have involvement of that total area, but many had small shadows scattered through that area. This also is true of the group of "not more than one lobe" cases. A case with small shadows through one lobe might, therefore, have a smaller total volume of involvement than one with heavy shadows above the first rib.

Another point of considerable interest to us is that many of the cases presented here did not have clinical tuberculosis, in other words, they fall into that group in Brown's⁵ classification of demonstrable non-clinical cases. Many of them gave no history of illness. Of this entire group, some were examined because they were applying for insurance or compensation, some were examined because they believe in periodic physical examinations, and others were examined because they showed definite symptoms. Of the entire group of 717 cases, 203 fell into the "above the first rib" group. The average vital capacity for this group was found to be 98.7 per cent of the theoretical normal. This figure is only slightly below that of 101 cases with negative roentgen-ray findings (Table 2).

TABLE 2.—Seven Hundred and Seventeen Cases Grouped According to Roentgen-Ray Findings

	Clinical Tuberculosis			Clinical Significance Questionable			Nonclinical Tuberculosis		
	No. of Cases	Average Vital Capacity	No. of Cases	Average Vital Capacity	No. of Cases	Average Vital Capacity	No. of Cases	Average Vital Capacity	
Negative	112	104.1							
Pleurisy (chronic fibrous)	54	94.1							
Fmpyema (healed)	26	91.0							
Pulmonary tuberculosis									
A Unilateral									
1 Above the first rib	203	98.7	42	85.5	9	89.0	152	103.0	
2 Not more than one lobe	91	90.5	38	87.5	7	92.1	49	103.7	
3 More than one lobe	22	65.6	22	65.6	None				
B Bilateral									
1 Above the first ribs	70	95.5	30	84.3	8	98.7	32	102.8	
2 Not more than two lobes	90	80.9	69	74.4	4	106.0	17	101.8	
3 More than two lobes	46	53.8	46	53.8	None				
Total	717								

Of the 203 cases, however, only forty-two had clinical disease. Their average vital capacity was found to be 85.5 per cent of the normal or more than 18 per cent lower than the group of 101 negative cases. Of the 203 cases, there were nine in whom the clinical significance was questionable at the time of the examination. They presented an average vital capacity of 89 per cent of the normal. Among the 203 cases, 152 fell into the class of demonstrable nonclinical disease. It was gratifying to us to find that this group possessed an average vital capacity approximately as high as the group of negative cases.

It is obvious, therefore, that it is never fair to the vital capacity test to present averages from cases grouped according to the roentgen-ray findings alone. The clinical significance of disease is of utmost importance. This holds true throughout the remainder of Table 2, which is

5 Brown, Laurason. Early Diagnosis of Pulmonary Tuberculosis, J. A. M. A. 78:79-84 (Jan 14) 1922.

self explanatory Small areas of nonclinical disease affect the vital capacity of the lungs very little or not at all On the other hand, our study leads us to believe that clinical tuberculosis practically always reduces vital capacity

At this point, attention must be called to one of the pitfalls in vital capacity work It is a well known fact that because of special previous development and training a considerable number of persons have vital capacities much greater than those indicated by our present normal standards Such persons may present capacities which appear to be above the normal but which in reality are definitely reduced Because of this fact, the vital capacity test can never be as useful as we should like to see it In other words, our normal standards can never be made to cover these exceptional cases any more than normal weight standards can ever cover unusual and exceptional cases In such cases, the vital capacity test is of great value if actual readings have been recorded while patients were in good health At any subsequent examination, a definite reduction in the vital capacity is of no little significance The following case illustrates this point

REPORT OF CASE

A man, aged 25, examined while apparently in good health, had a vital lung capacity of 5,000 cc, which was much beyond his theoretical normal The physical and roentgen-ray examination revealed no evidence of a pathologic condition of the chest A few months later, this man appeared for reexamination This time his general appearance had changed He looked ill His vital capacity was 2,500 cc—just half of his capacity when in good health Further examination revealed an extensive pleural effusion To be sure, this was easily detected by other means, but one occasionally encounters conditions less easy to detect, in which the vital capacity renders a very distinct service in diagnosis

In a few persons apparently in good health, the vital capacity is considerably below that which our present normal standards would indicate Although no cause can be found, it remains persistently low Here, again, vital capacity records previously made are of great value Although this ideal will never be reached, it is gratifying to know that many institutions, both educational and industrial, are making vital capacity records of their students and employes as a matter of routine Many practitioners of medicine are also making records of the vital capacities of their patients The recording of vital capacities probably will never become universal any more than the recording of body weights is universal, therefore, we will be compelled to use theoretical normal standards to a large extent We wish to encourage the recording of vital capacity as a routine matter in just as many persons as possible, as we are convinced that the test is worth while, and that serial readings bring out the greatest value of the test to the physician

NEPHROSIS

A CLINICAL AND PATHOLOGIC STUDY *

JOSEPH KAUFMANN, M.D., AND EDWARD MASON, M.D.
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The term nephrosis, introduced several years ago, was carefully studied by Volhardt, and later elaborated in the studies of Epstein, Eppinger and many other observers.

There is a type of disturbance in which one finds, as outstanding features, massive edemas and anasarca, low blood pressure, abundance of albumin in the urine, a urine of a high specific gravity, a urinary sediment that is rich in casts and shows a persistent absence of blood, and a kidney that shows essentially a degenerative process in the epithelial cells. This condition is clinically referred to as nephrosis. Further, we find that the urine contains globulin, there are no eye changes in the uncomplicated cases, the fundi remaining normal throughout the illness, there is a moderate but progressive anemia and an inability to excrete salt, the level of the plasma chlorids depends on the developing or eliminating of the edema, there is normal excretion of nitrogen end-products, normal blood nonprotein nitrogen, increase of cholesterol in the blood, a decrease in the total blood proteins, with a relative increase in percentage of globulin, edema fluids are rich in globulin, and there is a low basal metabolism (calculated on the false weight).

The foregoing clinical features might be considered as typical of a pure form of the condition from beginning to end, and establishes Type 1 of uncomplicated nephrosis.

CASE 1—*Type 1 Nephrosis*—R. E. B., a man, aged 29, was admitted to the Royal Victoria Hospital, Oct 22, 1923, and died, Feb 17, 1924. He was a farmer, and had been overseas, in France, four years during the World War.

He complained of swelling of the abdomen, legs and back, coughed, and had pain in his sides.

He had suffered with pyorrhea and bad teeth for several years preceding the onset of the present illness. He was in a hospital, in France, with this trouble, on one occasion for eight days, and on a second occasion for fourteen days. He was a chronic sufferer from sore throat July 16, 1923, after the extraction of several teeth, he first noticed a painless swelling of the external genitalia, which was later followed by swelling of the legs and back. He also had some headache. His appetite became poor. The swelling of the limbs became annoying. There was some frequency of micturition by day, but no night frequency. No disturbances of vision were noted. About the middle of September, the abdomen became greatly swollen, and he was very short of breath.

The patient had had no venereal disease. He was a moderate smoker, and did not use alcoholic beverages. He had been a hard laborer all his

* From the Royal Victoria Hospital

life He had had measles, whooping cough and chickenpox in early childhood The family history was good

Examination showed a well-developed man of good color, weighing 180 pounds (81.6 kg), with marked edema of the legs and thighs, ulcerated and decayed teeth, pyorrhea alveolaris, with evidence of abundant free fluid in the peritoneal cavity The liver and spleen were of normal size There was slight passive congestion of both lungs and moderate double hydrothorax There was a slight pericardial effusion, otherwise, the heart was normal The systolic blood pressure varied from 142 to 122, the diastolic, from 98 to 90

Blood examination revealed October 23, red blood cells, 5,400,000, white blood cells, 11,500, hemoglobin, 95 per cent, November 3, red blood cells, 5,300,000, white blood cells, 10,000, hemoglobin, 85 per cent, December 15, red blood cells, 5,100,000, white blood cells, 9,200, hemoglobin, 80 per cent, Jan 28, 1924, red blood cells, 4,720,000, white blood cells, 10,600, and hemoglobin, 75 per cent The blood smear was normal

The blood Wassermann reaction was negative, even after a provocative dose of neoarsphenamin The prostate showed a simple enlargement The remaining systems showed nothing of importance

The urine was turbid amber, specific gravity was 1.032, the albumin totaled from 5 to 8 gm a liter Microscopic examination showed coarse and fine granular and hyaline casts A phenolsulphonephthalein test resulted in the return of 34 per cent in the first hour, and 14 per cent in the second

TABLE 1—Blood Chemistry in Case 1

Date	Blood Urea, Gm per Liter	Creatinin, Mg per 100 Cc	Plasma Chlorids, Gm per Liter	Fundi
10/23/23	0.39	1.5	5.97	
10/27/23	0.46		6.22	
12/18/23	0.31	1.75		
1/ 4/24	0.24	1.52	6.138	
1/11/24	0.29	1.47	6.47	Normal
1/29/24	0.37	1.55	6.14	

Nov 5, 1923 globulin, 2.25 per cent, albumin, 3.48 per cent

hour, a total of 48 per cent in two hours This test was repeated and always showed a good output

Jan 12, 1924, the concentration of urea was 1.8 per cent in the second hour, and the factor, determined according to McLean, was 31.6 (slightly lowered)

January 7, the ascitic fluid showed 6.14 gm sodium chloride per liter

The Mosenthal test showed a fixed specific gravity of the urine at 1.020 The electrocardiogram showed a normal tracing The basal metabolism was minus 20 per cent (estimation on false weight) A roentgen-ray examination of the chest showed fluid at the bases of both lungs

The ordinary intake of fluids had varied from a minimum of 600 cc to a maximum of 1,300 cc The output varied from 2,030 cc, early after admission, to almost anuria, just before the patient's death

The temperature was normal, except toward the end, when he developed a terminal pneumococcal peritonitis, from which he died

The abdomen was aspirated six times between November 27 and February 12, a total of 25,260 cc of fluid being withdrawn, varying in color from a clear straw to turbid, and containing lymph flakes

The patient's condition went from bad to worse He developed a pneumococcal peritonitis, Feb 12, 1924, and died some five days later of respiratory embarrassment There was no coma Therapeutic measures, consisting of various diets and drugs, were all of no avail, and did not modify the course of the illness

The following is a brief summary of the positive findings which have a definite bearing on the case The onset was that of a renal disease with

gradually increasing edema and anasarca. The heart and blood vessels were normal. The blood pressure was normal. The urine showed a moderately high and fixed specific gravity and high albumin content, with abundance of casts but no blood. There was some secondary anemia. Blood chemistry showed a slight chlorid retention, otherwise, the findings were normal. The ratio of albumin to globulin in the blood was normal. The phenolsulphonephthalein output was only slightly impaired. The fundi were normal. Basal metabolism was low. The gums and teeth were diseased. Therapeutic measures were disappointing. The patient died with a terminal pneumococcus infection of the peritoneal cavity. There was no uremia. There were no signs of ruptured compensation.

The postmortem examination showed the following findings: degenerative and exudative nephritis, and pneumococcic peritonitis.

Other lesions were parenchymatous degeneration of the organs, hyperplastic splenitis, hydrothorax, hydropericardium, and anasarca.

Macroscopic examination of the kidneys revealed that the left kidney weighed 300 gm and the right kidney, 270 gm. In both kidneys, the capsule stripped with ease, leaving a smooth, pale surface with vascular markings. On section, the cortex bulged slightly and appeared swollen. The differentiation between the cortex and the medulla was fair. The surface showed reddish and yellow radiating streaks. The medulla was yellowish and appeared fatty.

When microscopic examination was made, the glomeruli appeared to be intact. The lumina of the tubules were dilated and filled with pale staining structureless material. Some of the tubular epithelium had desquamated, while the rest was granular and hazy in outline. The whole section appeared edematous, with an increase in size of the spaces between the tubules. There was little or no inflammatory exudate, and no increase in fibrous tissue. The blood vessels were dilated and filled with blood.

The second type of the same disease is one which, while retaining certain of the features of Type 1, has certain alterations as well as additions to the clinical picture. The blood pressure rises moderately, fundi changes develop, and the patient loses the ability to concentrate the urine (as in Type 1). There is an impairment in nitrogen excretion, and fat appears in the urine and ascitic fluid. Among the features of Type 1 which are retained are massive edema and anasarca, poor chlorid excretion, high cholesterol in the blood and high plasma and transudate chlorids.

CASE 2—*Type 2 Nephrosis*.—J. A. L., a man, aged 53, was admitted to the Royal Victoria Hospital Jan 4, 1924, and died February 16. He was a laborer, and had been in overseas service, in France, three years during the World War. His complaints were swelling of the abdomen, legs and arms, with headache, weakness and dry mouth.

In June, 1918, the patient was invalidated home from France on account of so-called chronic rheumatism. He worked very hard until December, 1921, but noticed during that time that his legs were swollen and that he was short of breath. Late in December, 1921, he was obliged to give up work because of these complaints. In January, 1922, he was admitted to the Western General Hospital, and remained there for five months, the condition having progressed. The abdomen and scrotum now became swollen, and he complained of great thirst and a dry mouth. Since leaving the hospital, he had been a confirmed invalid, although he was able to go for moderate walks. In December, 1922, he was readmitted to the hospital, and remained there for three months, without making any favorable progress. He left the hospital in February, 1923. He now complained of headaches more or less constantly. November,

1923, he took to bed on account of the increasing swelling of the legs Jan 4, 1924, he was admitted to the Royal Victoria Hospital. He was short of breath, complained of palpitation, coughed a good deal and vomited frequently. He had some night and day frequency.

The patient had had diphtheria, measles and whooping cough in childhood. He was a moderate smoker, and had been a heavy drinker of beer until 1920 (drinking from ten to fifteen glasses daily), but not since then. He said he had had no venereal disease. He had had rheumatism in the joints and muscles in 1918 (not acute rheumatic fever).

The father of the patient suffered from renal calculus, being 89 years old. The mother died of chronic interstitial nephritis at 36. The family history was otherwise negative.

Examination showed a well developed, large man, with pale skin and mucous membranes, marked edema of the legs and thighs, bad teeth and healthy gums. There was massive effusion into the peritoneal cavity and extensive edema of the abdominal wall. The rectum and the prostate were healthy. The liver and spleen were not palpated. There was some congestion of the lungs with double hydrothorax, slight hypertrophy of the heart and pericardial effusion. The systolic blood pressure varied from 194 to 170, the diastolic from 108 to 110. The blood showed a well marked secondary anemia with some anisocytosis and poikilocytosis. The differential blood count was normal.

TABLE 2—*Blood Chemistry in Case 2*

Date	Blood Urea, Gm per Liter	Creatinin, Mg per 100 Cc	Plasma Chlorids, Gm per Liter	Fundi
1/11/24	0.95	2.61	7.11	Albuminuric
1/24/24	1.03	3.15	6.62	retinitis
2/13/24	1.56	3.61		

Carbon dioxide capacity, 16 per cent by volume. Blood proteins total nitrogen, 0.77 per cent, nonprotein nitrogen, 0.13 per cent, globulin, 1.44 per cent, albumin, 3.06 per cent.

Blood examinations revealed January 20, red blood cells, 3,020,000, white blood cells, 13,400, hemoglobin, 60 per cent, January 25, red blood cells, 3,200,000, white blood cells, 9,750, and hemoglobin, 45 per cent. The blood Wassermann reaction was negative. The fundi showed a well marked albuminuric retinitis. The remaining systems showed nothing of importance.

The urine was dark amber, acid, the specific gravity was 1.022, the albumin +++. Microscopic examination revealed granular and hyaline casts, fat globules and a few pus cells. No blood was seen microscopically or chemically. A phenolsulphonephthalein test resulted in a return of 7 per cent in the first hour, and 5 per cent in the second hour, a total of 12 per cent in two hours. This test was repeated, a few days later, and showed a total output of 14 per cent in two hours.

The electrocardiogram showed a right sided preponderance.

Examination of the ascitic fluid revealed specific gravity, 1.020, a trace of albumin, globulin +, and chlorids +. A second paracentesis, eight days later, showed that the fluid in the main was the same, except that it contained a moderate quantity of neutral fat.

Cholesterol in the blood totaled 555 mg per hundred cubic centimeters. Ascitic fluid chlorids totaled 7.61 gm sodium chlorid per liter. The urea concentration and factor showed marked impairment.

There was a decrease in the total plasma proteins. The albumin-globulin ration was normal. The basal metabolism was minus 24.5 per cent (estimation on false weight). Roentgen-ray examination of the chest showed the heart transverse and moderately large. The ordinary intake of fluids varied from

775 cc to 1,200 cc, and the output varied from 1,450 cc to almost a complete anuria just before death. The temperature was normal during his entire stay in the hospital, in spite of the fact that, during the last ten days, he had a marked acute otitis media. The abdomen was aspirated three times between January 5 and 18. Fifteen thousand four hundred cubic centimeters of opalescent and at last almost milky fluid were withdrawn.

The patient's condition grew progressively worse. Therapeutic measures gave no relief whatsoever. The patient became uremic toward the end and died in coma.

The following is a brief summary of the positive findings, which have a definite bearing on this type of nephrosis. The onset was that of renal disease of some two years' standing with gradually increasing edema and anasarca. The heart showed some hypertrophy, and the blood pressure was elevated. Albuminuric retinitis was present. The urine output was moderate, the specific gravity was fixed, albumin was always abundant, and the sediment contained abundant hyaline and granular casts and fat, but no blood. The phenolsulphonephthalein output was greatly reduced. There was a marked retention of urea and creatinin, the chlorids in the blood were high, the chlorids and globulin in the ascitic fluid were high and the cholesterol in the blood was high. The ascitic fluid and urine contained neutral fat. The basal metabolism was low. There was a marked secondary anemia. There was a terminal acidosis. Therapeutic measures were of no avail. The patient developed uremia and died in coma. There were no signs of ruptured compensation. The postmortem examination was made one hour after death, and a report was returned of degenerative and productive nephritis. The subsidiary lesions were arteriosclerosis, hydrothorax, hydropericardium, ascites, anasarca and a terminal right upper lobar pneumonia.

Macroscopic examination of the kidneys revealed that the left kidney weighed 120 gm, the right kidney, 140 gm. The renal arteries were intact. The capsule stripped easily and showed a smooth surface of pale yellow. On section, the cortex bulged slightly and was pale in color, and the differentiation was poor. The cortex was narrow, 0.5 cm, with much peripelvic fat. Both kidneys showed the same condition.

Microscopic examination showed that many glomeruli were shrunken. Some showed synechiae, partial or complete. There was considerable edema of the tissues between tubules, with some fibrous tissue production. The tubules showed dilated lumina with low epithelium and many hyaline casts. Blood vessels were thickened, especially in the intima, and all were congested.

The third type represents all the stages of the disease.

CASE 3.—*Type 3 Nephrosis, Showing in Early Part of Illness Characteristic Picture of Type 1, and in Terminal Part, Picture of Type 2*—T. C., a man, aged 18, who had recently arrived from China, was admitted to the Royal Victoria Hospital, May 21, 1920, and died, Nov 29, 1922. He remained in the Royal Victoria Hospital under constant observation from the early onset of his illness until his death, with the exception of a few short intervals during which he was allowed to return to his friends. The complaints were swelling of the legs, body, hands and face, with weakness.

Following an attack of some febrile disturbance about one month before admission, the patient noticed that his feet began to swell. The swelling progressed rapidly up his trunk, arms and face, and he was obliged to give up work. There were absolutely no other symptoms or signs in the early development of his illness. He had been ill with boils on the neck, while in China, some years before, otherwise, his history was good. There had been no past illness of any importance. The family history was excellent.

Examination showed a poorly developed young Chinaman, very pale, weighing 153 pounds (69.4 kg.), with marked generalized edema, ascites and hydrothorax. Fifty per cent of the weight was fluid, as shown later by the true

weight when the edema was eliminated. The liver and the spleen were of normal size. The buccal cavity was healthy, and the heart was healthy. The systolic blood pressure was 110, the diastolic 65.

Urine examination gave specific gravity, 1.037-1.040, albumin, +++, as high as 24 gm per liter. The sediment was rich in casts, there was no blood. Oliguria was present day and night. There was an inability to excrete chlorids. The plasma chlorids were 58 gm per liter. The nonprotein nitrogen in the blood was normal. The urea was 0.39 gm per liter. The abdomen was tapped on several occasions, large quantities of clear, serous fluid being removed. On admission, the total plasma nitrogen was 0.74 per cent. The blood globulin was 2.08 per cent and the albumin, 1.40 per cent (reversed ratio).

Without any apparent reason, the anasarca began to clear gradually without any change in the albumin-globulin ratio. The blood pressure remained normal. The fundi were normal. July 28, 1920, the patient's weight, after the edema and anasarca had entirely disappeared, was 79 pounds (35.8 kg.) approximately half of what it was on admission.

The blood findings, when the anasarca was all gone, were as follows: total plasma nitrogen, 1.11 per cent, nonprotein nitrogen, 30 mg per hundred cubic centimeters, globulin, 3.4 per cent, and albumin, 2.7 per cent.

In spite of the disappearance of the anasarca, there was still a considerably greater amount of globulin than albumin in the blood.

During the stage of disappearance of the edema, the patient had a marked diuresis, as much as 2,700 cc of urine a day. When the diuresis started, the chlorids in the blood rose to 7.05 gm a liter (July 5, 1920). When the diuresis was completed, the chlorids in the blood were down to 5.9 gm a liter. The cause of the clearing of the edema was unknown. The patient failed to respond to all methods of treatment. With the onset of the illness, the chlorid output was less than 1 gm a day. When the edema was disappearing, he was putting out from 15 to 16 gm of chlorid a day. During all this time he was never given salt as such, the food containing roughly about from 1 to 2 gm of chlorids. He remained free from the edema for approximately three weeks, and, with apparently no cause, it recurred in the first week of August. Oliguria became a marked feature again, chlorid excretion dropped to 1 gm a day.

Plasma chlorids were 5.8 gm a liter, as at the onset of the illness.

The urine contained 30 gm of albumin to the liter and the other features were the same as at the beginning. The systolic blood pressure was 110, the diastolic, 70. The proteins in the blood were total plasma nitrogen, 0.91 per cent, globulin, 3.61 per cent, and albumin, 1.29 per cent.

As advised by Epstein, the patient was now fed on a high protein diet, 1,548 calories with 70 gm of protein. Previously, the diet had been kept at from 30 to 35 gm of protein. The calories given were largely in carbohydrate. The high protein diet resulted in nitrogen retention, the blood urea rising to 0.6 gm a liter. With the rise in the blood urea, the blood pressure rose also, the systolic being 130. The fundi remained normal. At this time the albumin-globulin ration was 1:1. The blood cholesterol was 500 mg per hundred cubic centimeters.

By the fall of 1921, the case presented features of nitrogen retention as well as chlorid retention, with greater inability to concentrate. The specific gravity kept at about 1.015. At this time, a definite creatinin retention developed, 2 mg per hundred cubic centimeters of blood.

Throughout the first half of 1922, the edema continued to fluctuate, the blood pressure gradually rising to a level of 180 systolic, 110 diastolic.

Creatinin retention developed to 5 mg per hundred cubic centimeters of blood. The plasma chlorids remained at from 6.2 to 6.5 gm a liter. Inability to concentrate became more marked, ranging from 1.010 to 1.012. The casts

and albumin stayed as before. The albumin-globulin ratio was normal. The anemia progressed. The red blood cells totaled 2,000,000, with hemoglobin, 50 per cent.

In the fall of 1922, the patient developed an acute bronchitis, which failed to clear up, and which was subsequently diagnosed as miliary tuberculosis. Death occurred, November 29, with a marked acidosis of 36 per cent by volume carbon dioxide (capacity).

It is interesting to note that this patient, in September, 1920, developed a renal glycosuria, having from 5 to 8 gm of glucose a day in the urine until death. At no time did the blood sugar rise above a normal figure, the average value being 0.08 per cent.

The following is a brief summary of the important findings in this case. The early stage of the illness clearly resembled Type 1. The findings were:

1 Edema and general anasarca

2 High and fixed specific gravity of the urine, which was very rich in albumin and in which the sediment contained a large number of hyaline and granular casts, but no blood.

3 Low blood pressure, the heart and blood vessels were normal.

4 A secondary anemia.

5 Blood chemistry showing a chlorid variation according to whether the edema progressed or diminished. Normal nonprotein nitrogen, with the globulin in the blood nearly twice the amount of albumin.

6 The fundi were normal.

7 Basal metabolism was low.

With the progress of the disease, other features developed closely resembling the well defined stages of Type 2.

1 Rising blood pressure.

2 Nitrogen retention.

3 Return of albumin-globulin normal ratio in the blood.

4 Retinal hemorrhages.

5 More marked anemia.

6 The urine showed a lowered specific gravity, the albumin and sediment remaining about the same. There was no blood.

7 The chlorid retention improved somewhat with the development of the nitrogen retention.

8 There were no signs of cardiovascular disease.

The following points are of special interest in connection with this case:

1 The disappearance of the edema without the alteration of the blood proteins.

2 The high protein diet resulted in nitrogen retention.

3 No red blood cells were found in the urine at any time.

4 Starting with a low blood pressure and a high urinary concentration, as the months passed, the blood pressure rose and inability to concentrate progressed.

5 Anemia progressed without remission.

6 The occurrence of renal glycosuria.

7 The immediate cause of death was an intercurrent infection.

The postmortem examination resulted in the following report. Productive nephritis (small white kidneys), generalized miliary tuberculosis (lungs, spleen, liver, kidneys, suprarenals, pancreas, bladder and peritoneum) and tuberculosis of mediastinal glands, edema, ascites and hydrothorax. There were numerous minor findings of no bearing on the case.

Macroscopic examination of the kidneys showed that the left kidney weighed 60 gm. The vessels were not markedly arteriosclerotic, the capsule was opaque, the cut surface was pale and greyish yellow, the cortex and medulla

were poorly marked, the cortex was very narrow, vascular markings were lost, the capsule was only slightly adherent, and when stripped left a moderately finely granular surface, studded with fine miliary tubercles. The right kidney was small, weighing 55 gm., of regular shape, the capsule was stripped easily, leaving a slightly rough surface studded with fine tubercles. The cut surface was pale, vascular markings were slightly more prominent than in the left kidney. The cortex was narrow, and in the periphery were several fused small areas between radiating vessels.

In the microscopic examination of the kidneys, the sections showed very widespread productive lesions, changes in the glomeruli were marked and showed all stages of thickening of the capsule, fibrosis and atrophy of the tufts of connective tissue between the tubules which, however, were more marked in some areas, producing a slight island appearance. Many of the tubules contained casts, hyaline, granular or cellular. The epithelium lining the tubules showed varying stages of granular degeneration. Definite scattered tubercles also were seen showing typical epithelioid proliferation, slight or early central necrosis and a very marked peripheral round celled infiltration.

A brief clinical study of this case shows conclusively that in the early stage of the illness the patient suffered from a typical nephrosis resembling in most details that of Type 1. In the later and last stages of the illness, the picture changed somewhat, while still retaining some of the features of Type 1, there were definite evidences of clinical changes and blood chemistry of Type 2. In short, we have both types well and clearly exemplified in one patient, showing that if the patient lives long enough, one type of the disease will progress into the second type and the gross and microscopic changes in the kidneys will go hand in hand with the clinical progress and blood chemistry alterations. We are dealing in this case, then, with one disease entity, both in its early and in its late stages, the kidney changes being merely evidences of a later stage of the organ in the progress of the illness. It would seem that the condition of the kidney depends essentially on the supervention of the intercurrent fatal infection.

SIMILARITY OF TYPES

A careful clinical study of our cases reveals the following points of interest in all of them:

- 1 The edema was massive, and one may say that an early general anasarca was the rule. All cases had effusion into the potential serous cavities.
- 2 Albumin in the urine was very abundant, going up to 30 gm. a liter.
- 3 The specific gravity was, generally speaking, high in the early stages, progressing to a low level as contraction of the kidney developed.
- 4 Blood was absent in the urine.
- 5 Urinary sediment was rich in casts, especially of the hyaline and granular varieties.
- 6 The output of urine was small, as a rule, always less than 1,500 cc., save when powerful diuretics were used, and even then seldom exceeded 2,500 cc. on more than one or two occasions.

7 Chlorids in the urine were low

8 Plasma chlorids fluctuated according to the degree of anasarca present

9 Urea and nitrogen disturbances in the blood and urine were not much affected when the principal feature of the disease was the nephrosis of Type 1. With contraction of the kidneys (Type 2), nitrogen retention developed

10 Fundi were normal in early cases, but hemorrhages and retinitis were encountered in the later stages

11 The early cases showed a normal or low blood pressure, while the late forms showed high blood pressure

12 All our cases had few or no objective or subjective signs of cardiac embarrassment, nor did the postmortem examination show evidences of a failing cardiovascular system

13 Cholesterin in the blood was increased, and neutral fat was present in the ascitic fluid and urine

14 Therapeutic results were only temporarily beneficial

Pure forms of nephrosis, the so-called textbook picture, are uncommon. Combination forms, with productive or exudative changes superadded, are more common. The combination forms usually have a high blood pressure, albuminuric retinitis and urea retention. When the nephrosis is the important feature, we find that the specific gravity of the urine is fixed and at a higher level, and albumin is more abundant than one finds in the kidneys in cases of chronic nephritis or of heart disease. In the combination forms, we find the edema very early, and we cannot attribute it to the defective cardiac function.

COMMENT

Is nephrosis a renal disease entity, or is it a local manifestation of a general systemic disturbance?

It would appear that the edema has little relation to the kidneys, but that it depends on an altered state of capillary permeability. The cause of this increased permeability is unknown. It may be toxic or it may be nutritional. We believe that nephrosis, as applied to the kidneys, is an early manifestation of a general systemic cellular degenerative process of unknown origin.

It is interesting, in this connection, that these patients show a lowered basal metabolism, which would have to be classified as a secondary hypothyroidism. Their thyroids can manufacture thyroxin at a normal rate, but, due to the lack of tissue call, the thyroxin content of the tissues falls below normal. This results in altered cellular nutrition.

The evidence at our disposal indicates that the true nephrotic kidney progresses into the secondary contracted type as a result of an organizing process of the degenerated cells, and not as a primary inflammatory entity.

The pathologic findings, in the different cases, vary according to the stage in the disease at which death occurs.

THE EXCRETION OF ORGANIC ACIDS AFTER PNEUMONIA *

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ST LOUIS

In this paper, it will be shown that large quantities of organic acid are excreted in the urine after the crisis in pneumonia

The patients studied ranged in age from 16 months to 14 years. Eight were typical lobar pneumonia patients, two had bronchopneumonia following influenza. The total quantity of urine in twelve hours was collected, preserved with toluene and kept on ice until analyzed. Analytic methods were (a) determination of total organic acids by the method of van Slyke and Palmer,¹ and (b) the determination of ether soluble acids by the following method. Two cubic centimeters of urine was placed in a test tube, 1 gm of solid ammonium sulphate and 1 drop of concentrated sulphuric acid were added. The ether soluble acids were removed in the continuous ether extractor recently described.² Occasionally emulsions formed, and the results of analysis were liable to be too high. No result was accepted when sulphate could be demonstrated in the ether extract by means of barium chloride. The ether extracts in the Kjeldahl flasks were evaporated to a small volume and titrated with carbon dioxide-free twentieth normal sodium hydroxide. The results of all analyses are expressed in terms of tenth normal acid.

Data are presented in the tables which give the patient's weight, the date of onset and the duration of the pneumonic process. The columns in the tables give date, volume of urine, acid as determined by van Slyke's method, ether soluble and ether insoluble acid (determined by difference) and the maximum daily temperature. It will be seen that the excretion of organic acid is considerably in excess of the normal figure (from 8 to 11 cc per kilogram a day) given by van Slyke. The maximum excretion of organic acid occurs from one to four days after the crisis. In cases of lysis (Case 10, E W), the maximum is not strikingly high. In certain other cases, however, the maximum is exceedingly high (from three to eight times the normal). It will be seen that this maximum corresponds only roughly to the period of

* From the department of pediatrics, Washington University School of Medicine, and the St Louis Children's Hospital

1 Van Slyke, D D, and Palmer, W W Titration of Organic Acids in Urine, *J Biol Chem* **41** 567 (April) 1920

2 Clausen, S W A Method for the Determination of Small Amounts of Lactic Acid, *J Biol Chem* **52** 263 (May) 1922

maximum diuresis In general, the maximum excretion of ether soluble acids coincides with that of the ether insoluble acids It is to be noted, however, that ether insoluble acids comprise by far the greatest part of this maximum excretion Furthermore, the period of maximum excretion corresponds to the period of resolution of the pneumonic process, as determined clinically

Efforts are being made to determine the nature of the ether insoluble acids The nature of the ether soluble acids also is as yet undetermined It is likely that acetone body acids make up only a small proportion of the total, the ferric chloride reaction in most cases being only slightly positive and then only during the febrile stage

In order to get some idea of the nature of the ether soluble acids, use was made of their distribution ratio between water and ether The ether extract from a considerable quantity of urine was titrated with saturated barium hydroxide, any precipitate (containing such barium salts as the sulphate, carbonate, phosphate or oxalate) was removed by filtration The filtrate was evaporated to a small volume, and reextracted with ether This second extraction was performed in steps, adding at each step one fifth of the quantity of sulphuric acid calculated to neutralize the entire amount of barium It is obvious that those acids which are "weaker" will be liberated first, since these are, in general, more readily soluble in ether, the successive fractions will represent a fairly good separation Each ether extract was shaken with water at 20 C, and the concentrations of acid in the water and in the ether were determined by titration with the carbonate-free twentieth normal sodium hydroxide The concentration in ether will, under these circumstances, depend only on the concentration in the water, and will be independent of the total quantity of water, ether or acid, and will be affected only slightly by small amounts of other substances Moreover, the ratio of concentrations is nearly, but not quite, independent of the actual concentrations By this procedure, it is possible to demonstrate in normal urine and in the urine from patients with pneumonia, at least two ether soluble acids

TABLE 1—Ratio of Concentrations

	Extract Number 1	Extract Number 2	Extract Number 3	Extract Number 4	Extract Number 5
Normal Urine					
Molar concentration in ether	0.024	0.0192	0.0295	0.0078	0.001?
Molar concentration in water	0.067	0.037	0.075	0.053	0.006?
Ratio	0.36	0.83	0.168	0.148	0.15?
Pneumonic Urine					
Molar concentration in ether	0.015	0.0118	0.0126	0.0062	
Molar concentration in water	0.040	0.0566	0.102	0.049	
Ratio	0.375	0.208	0.124	0.126	

Acids with distribution ratios near those found for urinary acids in the concentration range in question are citric acid, with a ratio of 0.023, lactic acid, with a ratio of 0.10, formic acid, ratio, 0.12, oxalic acid, ratio, 0.13, betahydroxybutyric acid, 0.40, acetic acid, 0.47, propionic acid, 1.8, and n-butyric acid, 3.4

TABLE 2—*Findings in Case 1*

Weight, 10 kg, onset, February 7, crisis, seventh day

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 12	620	266	31	235	40.4
February 13	730	242	43	199	40.2
February 14	535	230	44	186	39.8
February 15	540	418	63	355	38.6
February 16	1,160	908	50	258	38.7
February 17	435	321	19	302	38
February 18	555	127	23	104	38
February 19	510	118	33	85	38.8

TABLE 3—*Findings in Case 2*

Weight, 25 kg, onset, February 17, crisis, seventh day

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 24	154	210	18	192	40.2
February 25	340	496	74	122	38
February 26	350	1,188	41	1,147	37
February 27	187	469	32	437	37.5
February 28	500	210	26	184	38

TABLE 4—*Findings in Case 3*

Weight, 20 kg, onset, February 1, crisis, sixth day

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 7-8	700	241	71	170	39.5
February 8-9	385	221	57	164	37.4
February 9-10	515	300	80	220	37.1
February 10-11	910	389	100	289	36.8
February 11-12	1,155	512	66	446	37
February 12-13	520	282	32	250	37.6

TABLE 5—*Findings in Case 4*

Weight, 56 kg, onset, February 15, crisis, sixth day

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 20	1,990	834	210	624	40.2
February 21	1,260	755	155	600	39
February 22	1,760	740	158	582	38
February 23	2,670	1,330	193	1,137	27.8
February 24	2,140	950	148	702	37.6
February 25	820	514	160	354	37.6
February 26	260	187	32	155	37.6
February 27	1,380	762	186	576	37.6
February 28	830	252	51	201	37.6
March 1	1,070	369	63	306	37.5
March 2	1,460	850	190	660	37.4

TABLE 6—*Findings in Case 5*

Weight, 22 kg onset, February 6, crisis, fourth day

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 9	265	351	140	215	40.4
February 10	458	340	54	286	39.3
February 11	340	165	35	130	37.8
February 12	360	189	52	137	37.5
February 13	460	564	58	506	37
February 14	360	457	128	329	37.2

TABLE 7—*Findings in Case 6*

Weight, 23 kg, onset, February 1, crisis, seventh day

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 7-8	270	236	14	222	40.6
February 8-9	258	245	46	199	38.6
February 9-10	255	484	73	413	36.8
February 10-11	918	593	71	522	36.8
February 11-12	555	412	78	334	37

It will be seen that the ether soluble acids in pneumonic urine may include formic, lactic, betahydroxybutyric, acetic, and probably others. Any oxalic acid present would have been precipitated by the barium hydroxid. Direct determinations show the absence of any large quantity of lactic acid in the urine in these cases.

TABLE 8—*Findings in Case 7*

Weight 22.7 kg onset February 1 crisis, sixth day

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 8	550	335	57	268	37.6
February 9	115	213	26	187	37.2
February 10	310	554	53	501	37.4
February 11	920	470	114	356	37
February 12	655	318	90	228	37.1

TABLE 9—*Findings in Case 8*

Weight, 8 kg, onset, February 22(?) crisis seventh day

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 27	225	154	28	131	39.2
February 28	250	590	32	558	39.4
March 1	200	624	24	610	38.2
March 2	102	96	12	84	37.8
March 3	210	89	13	76	37.2
March 4	80	120	6	14	38.2

TABLE 10—*Findings in Case 9*

Weight 6 kg, onset, February 20, crisis, fifth day

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 24	370	86	20	663	40
February 25	675	390	117	273	38.8
February 26	340	230	48	242	36.4
February 27	400	233	46	187	36.8
February 28	350	138	21	117	37.8
March 1	220	153	30	123	38.6

TABLE 11.—*Findings in Case 10*

Weight, 30 kg., onset (✓), no crisis

Date	Volume	Total	Ether Soluble	Ether Insoluble	Temperature
February 25	1,000	498	110	388	38.8
February 26	440	433	56	376	38.6
February 27	1,100	477	113	333	38.2
February 28	1,420	500	68	432	37.8
March 1	970	372	44	328	37.4
March 2	510	240	25	215	37.6
March 3	980	390	103	287	37.4
March 4	550	330	55	275	37.2

CONCLUSIONS

- 1 Large quantities of organic acids are excreted in the urine after pneumonia
- 2 The period of maximum excretion corresponds to the period of resolution
- 3 The larger part of the organic acids excreted during resolution in pneumonia is insoluble in ether

THE ALKALINE TIDE IN ACHLORHYDRIA *

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It has been generally believed that the changes in the reaction of urine which occur after a meal are due to the secretion of hydrochloric acid by the stomach and its subsequent reabsorption in the intestines. This view has been opposed by Hasselbalch¹ and by Leathes,² but has been supported by the more recent work of Campbell³ and Fiske⁴. The earlier literature has been reviewed in these articles, in an article by us,⁵ and in a discussion of the acid-base balance by Wilson,⁶ therefore, it does not seem necessary to discuss it again at this time.

The method of fractional gastric analysis proposed by Rehfuss, Bergeim and Hawk,⁷ in 1914, has recently been subjected to criticism. Gorham,⁸ in 1921, first showed that there were marked differences in the acid content of samples of gastric juice obtained from different parts of the stomach, and questioned whether this should not make the clinical interpretation of the results doubtful. Considerable literature, for the most part confirmatory of his results, has appeared since his publication, and although Rehfuss⁹ has called attention to the fact that the method

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¹ A preliminary report of a part of this work was read before the American Society of Gastro-Enterology, May 6, 1924.

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² Leathes, J B Renal Efficiency Tests in Nephritis and the Reaction of the Urine, Brit M J **2** 165 (Aug 9) 1919

³ Campbell, J A Ammonia Excretion, Amino-Acid Excretion, and the Alkaline Tide in Singapore, Biochem J **14** 603, 1920

⁴ Fiske, C H Observations on the "Alkaline Tide" After Meals, J Biol Chem **49** 163 (Nov) 1921

⁵ Hubbard, R S, and Munford, S A The Excretion of Acid and Ammonia, J Biol Chem **54** 465 (Oct) 1922

⁶ Wilson, D W Neutrality Regulation in the Body, Physiol Rev **3** 295 (July) 1923

⁷ Rehfuss, M E, Bergeim, O, and Hawk, P B Gastro-Intestinal Studies, II, The Fractional Study of Gastric Digestion with a Description of Normal and Pathologic Curves, J A M A **63** 909 (Sept 12) 1914

⁸ Gorham, F D Variations of Acid Concentration in Different Parts of the Gastric Chyme and Its Relation to Clinical Methods of Gastric Analysis, Arch Int Med **27** 434 (April) 1921

⁹ Rehfuss, M E Diagnosis of Gastric Disease, Ann Clin Med **2** 55 (July) 1923

has been used with general success in clinical work, and that this proves its value, still the bulk of the evidence tends to show that the results in any given case may be open to considerable suspicion¹⁰. It has seemed worth while to try to find some method for the study of gastric secretion by which gastric analyses in doubtful cases might be confirmed. If a method can be found which will agree, even approximately, with the fractional analysis, it should be useful, not only for this purpose, but also for getting information in cases in which gastric analyses cannot be obtained. With this end in view, a study of the alkaline tide in urine was undertaken.

In an earlier paper from this clinic,¹¹ it was found that the alkaline tides showed variations after meals containing different kinds of food-stuffs similar to those which can be demonstrated in the acidity of the gastric juice, and that in seven cases without hydrochloric acid in the stomach the tide was either absent or markedly decreased. These facts seemed to warrant further study of the method with a view of applying it as an aid in diagnosis. The present paper has been devoted to collecting data on patients with and without acid in the gastric juice, for it is on material of this kind that clinical applications of the test must be based.

A study was made of patients on whom the results of gastric analyses by the method of Rehfuss, Bergeim and Hawk⁷ were available. No attempt was made to select patients, except that more pains were taken to secure urines from those in whom an achlorhydria or a very marked hypochlorhydria was found than from others, for results previously obtained¹¹ made it seem probable that the method might serve to pick out cases of this kind, but that it would not be delicate enough to differentiate cases with hyperchlorhydria from others. Since it was intended to apply the results to the study of clinical problems, it seemed best to carry out the tests in as nearly a routine manner as was possible. No attempt was made to secure duplicate determinations, for it is more important to know what reliance can be placed on the result of a single test than to know how good agreement can be shown under especially favorable conditions. Furthermore, it did not seem proper to repeat determinations which were probably open to suspicion, when it was not possible to repeat all. The gastric and urine tests were not carried out simultaneously, because the test was intended to be used in some cases in which gastric studies could not be obtained, and it is by no means improbable that the removal of part of the stomach contents affects the

10 Friedenwald, J. G., Gantt, N. H., and Morrison, T. H. Studies in Fractional Analysis, *Ann Clin Med* **2** 292 (March) 1924.

11 Hubbard, R. S., Munford, S. A., and Allen, E. G. Gastric Secretion and the "Alkaline Tide" in Urine, *Am J Physiol* **68** 207 (April) 1924.

rate of reabsorption of acid in the intestine and its subsequent excretion in the urine.

Since it has been shown that the foods eaten in the meal influence the form of the alkaline tide, it is necessary to select a standard breakfast. The one used consisted of two slices of toast, an egg, a pat of butter, a glass of milk and a glass of water. Nothing else was taken during the test, for it has been shown that a secretion of acid is brought about simply by drinking water.¹² This breakfast was the one called the "standard" in the previous work. It caused the development of a less marked tide than did those high in protein, and of a more marked one than did breakfasts which consisted almost entirely of carbohydrate. Each patient began the test at 7 o'clock in the morning by emptying the bladder. Hourly specimens were then collected until 12 or 1 o'clock. Breakfast was given from 8:15 to 8:45. There were available for study a specimen collected before breakfast, one which corresponded to the

TABLE 1.—*Average Values*

Studied	Normal pH 7.0	Hydrochloric Acid Present		Hydrochloric Acid Absent		Hydro- chloric Acid Low pH 7.0
		All	pH 7.0	All	pH 7.0	
Number of determinations	8	45	35	18	16	6
Number of patients	3	45	35	18	16	6
Number of women	0	33	25	12	10	4
Time	pH	pH	pH	pH	pH	pH
1 hour before meal	5.7	6.4	6.0	6.5	6.2	6.4
1 hour at meal time	6.0	6.5	6.1	6.3	6.2	5.5
1 hour after meal	6.7	6.3	6.0	5.9	5.7	5.4
2 hours after meal	6.9	6.8	6.5	6.0	5.8	5.6
3 hours after meal	6.4	6.8	6.6	5.9	5.7	5.4
4 hours after meal	5.7	6.0	5.5	5.8	5.7	5.4

time at which the meal was eaten, and three or four obtained later. The hydrogen ion concentration of each was determined, as soon as possible after it was obtained, by a colorimetric method approximately the same as that described by Marshall,¹³ with standards prepared from a buffer solution described by Acree and his co-workers.¹⁴ Specimens were not collected directly in narrow cylinders, as recommended by Marshall, each was collected in the usual way and sent to the laboratory in a quart jar under toluene.

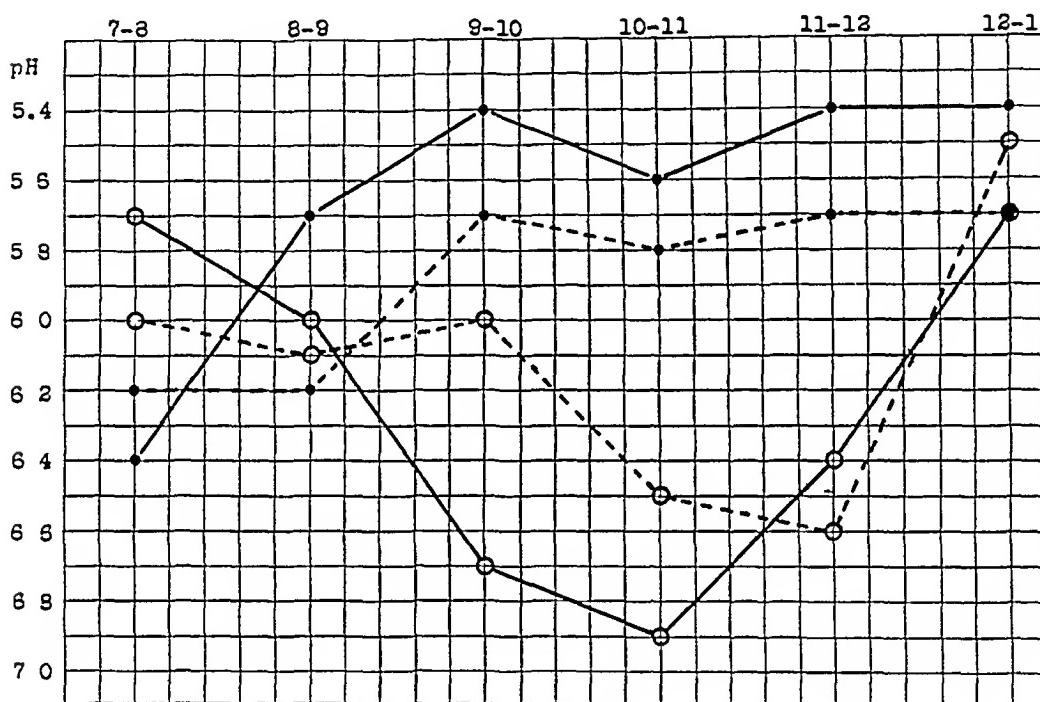
Table 1 shows the averages of all the results obtained. The normal subjects were three men laboratory workers in whose gastric contents

12 Bergeim, O., Rehfuss, M. E., and Hawk, P. B. Gastro-Intestinal Studies III (Studies of Water Drinking, XXI), Direct Demonstration of the Stimulatory Power of Water in the Human Stomach, *J. Biol. Chem.* **19**: 345, 1914.

13 Marshall, E. K., Jr. The Effect of Loss of Carbon Dioxide on the Hydrogen Ion Concentration of Urine, *J. Biol. Chem.* **51**: 3 (March) 1922.

14 Acree, S. F., Mellon, R. R., Avery, P. M., and Slagel, E. A. A Single Stable Buffer Solution, *J. Infect. Dis.* **29**: 7 (July) 1921.

hydrochloric acid had been demonstrated, and the others were patients from the clinic. Four of the determinations on the normal subjects were included in an article previously published.¹¹ It has seemed best, since Marshall¹² has shown that the results of hydrogen ion determinations on urine specimens which are alkaline are open to question, and since a considerable number of the subjects excreted urines which were alkaline or nearly alkaline throughout the test, to show not only the results from all cases but also those from cases in which the average p_H was less than 7.0. The table also includes a few experiments on subjects with very little acid in the gastric juice.



A (solid line, hollow dot), normal, eight determinations, three subjects; B (broken line, hollow dot), hydrochloric acid present, thirty-five determinations; C (broken line, solid dot), hydrochloric acid absent, sixteen determinations; D (solid line, solid dot), hydrochloric acid low, six determinations.

The results from subjects who did not excrete a very alkaline urine are given in the accompanying chart. The normal controls and patients in whose gastric juice acid was found showed typical alkaline tides, that is, the specimens collected in the middle of the morning were more alkaline than were those collected before or during the meal, and the reaction of the last specimen was more acid than were those of specimens collected earlier. No such tides were shown by the average figures from patients with achlorhydria or with very little acid in the stomach. These averages conform with the theory that the secretion of the gastric juice is the cause of the alkaline tide, as do results of similar alveolar air

studies by Bennett and Dodds¹⁵ They suggest that such urine studies may be of use in distinguishing cases with little or no acid in the gastric juice from those in which more acid is secreted

In Table 2, detailed data of all patients secreting little or no hydrochloric acid are given. Only those cases have been included in which the amount of acid was so small, or the length of time when the acid was present was so short, that it was practically impossible that the secretion and reabsorption of it could have had any effect on the excretion of acid in the urine. In one of these six cases, a definite tide was present, but in the others there was none found, as would be expected from the gastric analyses. The percentage of cases in which the two tests agreed is the same as that found in the series as a whole, as will

TABLE 2.—Results of Studies on Patients with Very Little Hydrochloric Acid

Time	RESULTS OF GASTRIC ANALYSES					
	Cc Tenth Normal Hydrochloric Acid in 100 Cc Gastric Contents					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Residuum	0	0	0	0	6	5
30 minutes after meal	2.5	0	0	0	0	21
45 minutes after meal	10	0	0	0	0	11
1 hour after meal	0.5	0	0	10	0	0
1 hour 15 minutes after meal	0	8	7	26	0	
1 hour 45 minutes after meal	0	0	0	0	0	
2 hours 15 minutes after meal	0	0	0	0	5	
2 hours 45 minutes after meal	0	0	0	0	0	

Time	ALKALINE TIDE STUDIES					
	Hydrogen Ion Concentration of Urine Specimens					
	pH	pH	pH	pH	pH	pH
Before meal	6.8	5.6	7.0	5.7	7.0	6.5
At meal time	4.9	5.3	5.8	5.6	7.7	5.9
1 hour after meal	4.9	5.3	5.2	5.5	5.3	6.3
2 hours after meal	4.9	5.4	6.8	5.0	5.3	6.3
3 hours after meal	5.0	5.2	6.5	4.9	5.0	5.7
4 hours after meal		5.4	6.5	4.8	4.8	

be shown here. The table shows that the absence of a tide is not diagnostic of a condition of achlorhydria, but it does confirm the impression that the gastric secretion is the cause of the alkaline tide.

The eight determinations on three normal subjects are given in Table 3. There were rather marked differences in the curves obtained from the same subject at different times, but the general form of each was similar to that of the average of the normal values. In the experiment in which the reaction of the first specimen was least acid, that on Case 1 in Table 3, July 10, although the differences in reaction between it and subsequent specimens were diminished, the general form of the curve resembled the others. It seems to the authors that such a find-

15 Bennett, T. I., and Dodds, E. C. The Gastric and Respiratory Response to Meals, *Brit. J. Exper. Path.* 2: 58 (April) 1921.

ing should not be unexpected when the acidity of the first specimen is low. The fact that other studies on this case showed unmistakable tides suggests that, if the reaction of the first specimen in a test is not very acid, it may be worth while to repeat the test to see whether results which are more easily interpreted can be obtained.

If the results are to be used in differentiating cases with little or no hydrochloric acid from those in which acid is present, it is desirable that a definition of what changes in reaction constitute a tide shall be given. It has not been found possible to do this in an entirely satisfactory manner. Two factors must be considered in judging each case. One is the difference in the reactions of different specimens, and the other is the relationship which the reactions of different specimens bear to each other. Sometimes the differences in reaction are small, but the relationship between the values shows that a tide is present. A good illustration of this is the experiment on Case 1, July 10, recorded in Table 3. Sometimes there may be a great difference between the

TABLE 3.—*Alkaline Tide Determinations on Normal Subjects*

Time	Case 1				Case 2		Case 3	
	7/6/23		7/10/23		6/27/23		7/5/23	
	pH	pH	pH	pH	pH	pH	pH	pH
1 hour before meal	5.4	6.6	5.7	5.6	5.5	5.5	5.9	5.7
1 hour at meal time	5.6	6.9	5.8	5.7	6.2	5.9	6.8	6.1
1 hour after meal	6.2	6.9	6.5	6.9	7.4	6.9	6.9	6.3
2 hours after meal	6.0	7.2	6.7	6.6	7.4	6.9	7.1	7.0
3 hours after meal	5.8	6.5	6.6	5.7	7.0	6.7	5.9	6.8
4 hours after meal	5.8	6.0	5.7		6.3	6.4	5.4	6.1

reactions of two specimens, and yet a study of the curve as a whole shows almost certainly that no tide is present. An example of such a result is shown in the second case in Table 4. In general, each test must be judged more or less on its own merits, and, if doubt is entertained about the meaning of the results, a duplicate study should be sought. In spite of these objections, we have formulated a definition as a basis for discussing the results. This definition, with some of the reasons which have influenced us in using it, is given below.

It has been shown, by Leathes,² by Collip and Backus¹⁶ and by Grant and Goldman,¹⁷ that a marked increase in the rate of respiration causes the excretion of an alkaline urine. Care was taken to prevent the occurrence of errors from this source, but as the effect of moderate changes of the respiratory rate cannot be determined, it has seemed

16 Collip J B and Backus, P L. The Effect of Prolonged Hyperpnea on the Carbon Dioxide Combining Power of the Plasma, the Carbon Dioxide Tension of the Alveolar Air and the Excretion of Acid and Basic Phosphate and Ammonia by the Kidney, *Am J Physiol* **51** 568 (April) 1920.

17 Grant, S B, and Goldman A. A Study of Forced Respiration, Experimental Production of Tetany, *Am J Physiol* **52** 209 (June) 1920.

best not to accept small changes in reaction shown by one specimen as indicating the presence of a tide. Another difficulty arises from the form of the curves observed in a number of instances. In the normal subjects, the reactions of the second, third, fourth and fifth specimens were more alkaline than was that of the first one. In many studies on patients, the findings were similar, but in some, the curves were like that shown by Case 6 in Table 2. There was a low degree of acidity in the specimen obtained before breakfast, a more acid reaction in the one collected at breakfast time, and a definite tide later, with values very little, if any, more alkaline than were those of the first specimen. It is possible that the secretion of acid by the stomach is responsible for this, for the presence of hydrochloric acid in the fasting contents, lower acid concentrations during the hour following the meal, and more acid

TABLE 4—*Cases with Achlorhydia Which Showed an Alkaline Tide*

Time	RESULTS OF GASTRIC ANALYSES		
	Case 1	Case 2	Case 3
Residuum	10	4	4
30 minutes after meal	8	3	6
45 minutes after meal	11	5	7
1 hour after meal	15	8	7
1 hour 15 minutes after meal	16	15	9
1 hour 45 minutes after meal	18	18	6
2 hours 15 minutes after meal	13	14	

Time	ALKALINE TIDE STUDIES		
	Hydrogen Ion Concentrations		
Before meal	pH	pH	pH
At meal time	6.0	8.4	5.6
1 hour after meal	6.6	7.9	6.4
2 hours after meal	5.8	5.4	5.6
3 hours after meal	6.0	7.1	6.5
4 hours after meal	6.9	5.7	6.6
	7.0	4.9	6.7

values later were not infrequent findings, the gastric curve of Case 6 in Table 5 may serve as an example of such determinations. Leathes,² however, has claimed that there is a retention of carbon dioxide during the night and a loss of that compound immediately after rising because of the increased activity of the subject and the consequent increase in the rate of ventilation. This increased rate of ventilation causes a tendency toward the secretion of an alkaline urine, just as did the experiments on hyperpnea already mentioned. It seems possible that such a process of readjustment as this might account for the low acidity of the first specimen with a subsequent excretion of a more strongly acid urine sometimes observed. Whatever is the cause of these variations in the first two hours of the test, the fact that they occur makes it seem inadvisable to consider the reaction of the specimen collected before breakfast as the only one with which those of later specimens is compared.

The criteria finally adopted for determining whether or not there was a tide in a given case were as follows. If any specimen was more alkaline than one collected earlier in the test by 1 p_H or more, or if any two were more alkaline by 0.5 p_H , we considered that a tide was present. The application of this can be seen in Table 4. The fourth specimen in the second case was more alkaline than the third by 1.7 p_H , and in the third case the fourth and fifth specimens were more alkaline than were the first and third by more than 0.5 p_H . Therefore, we consider that a tide was present in both of these cases.

When the cases were judged by the test proposed, it was found that the presence and absence of a tide agreed with the results of the frac-

TABLE 5.—*Cases with Hydrochloric Acid in the Gastric Juice Which Showed No Alkaline Tide*

RESULTS OF GASTRIC ANALYSES

C c Tenth Normal Hydrochloric Acid in 100 C c
Gastric Contents

Time	C c Tenth Normal Hydrochloric Acid in 100 C c Gastric Contents						
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Residuum	0	20	19	23	0	19	0
30 minutes after meal	0	10	21	62	0	23	33
45 minutes after meal	16	25	38	45	22	0	48
1 hour after meal	26	31	40	39	44	0	49
1 hour 15 minutes after meal	29	35	42	52	22	7	62
1 hour 45 minutes after meal	20	35	50	45		30	16
2 hours 15 minutes after meal		24				16	
2 hours 45 minutes after meal						25	
3 hours 15 minutes after meal						30	

ALKALINE TIDE STUDIES

Hydrogen Ion Concentration of Urine Specimens

Time	Hydrogen Ion Concentration of Urine Specimens						
	p_H	p_H	p_H	p_H	p_H	p_H	p_H
Before meal	5.9	5.2	5.7	6.1	6.7	5.0	5.3
At meal time	5.8	5.0	5.5	6.2	6.2	5.8	5.8
1 hour after meal	5.1	5.2	5.3	5.7	5.7	5.2	5.5
2 hours after meal	5.2	5.1	5.6	5.8	5.8	5.5	5.3
3 hours after meal	5.8	4.9	5.4	6.3	5.6	5.8	5.2
4 hours after meal	5.4	4.9	5.5	5.9	5.2		5.8

tional gastric analyses in 80 per cent of them. Table 4 gives detailed results on the gastric and tide tests in the cases of achlorhydria which showed a tide, and Table 5 gives similar data on the cases when hydrochloric acid was present but which failed to show one. In some of the cases included, the general impression given by the findings does not agree with the decision based on an arbitrary application of our standard, if such results had been met with in tests carried out for diagnostic purposes, we should have tried to secure another test as a check on them. Another factor which may have produced discrepancies is the variations in the results of the determinations which occur from day to day. It has been shown in the present paper that this is true of the alkaline tide tests, and the same thing has been shown to apply to gastric analyses.

also¹⁸ Repeated determinations of gastric analyses and urine studies would have helped in eliminating such sources of error, but, as already stated, it did not seem best to make them. It has seemed better to accept a discrepancy of 20 per cent between the results of the two tests rather than to press explanations of the failures.

Another factor which may sometimes affect the results remains to be discussed. It is not certain what effect damage to the kidneys may have on the alkaline tide.² The literature dealing with the effect of nephritis on the reaction of the urine has recently been reviewed by Rabinowitch¹⁹ and by Stieglitz²⁰. It has been shown by them, and by the authors whom they cited, that nephritis does influence the excretion of acid. It does not seem unlikely that the differences between the reactions of different specimens would also be influenced by kidney damage. It seems probable to the authors that the effect would be to decrease these differences. No direct evidence on this point was obtained, for no patients with severe nephritis were studied. We have found normal rates of the excretion of phenolsulphonephthalein in some of the cases of achlorhydria in which a tide was absent, and have occasionally observed considerable differences in the reactions of different specimens of urine from nephritic patients. In spite of these observations, a possible effect of kidney disease on the alkaline tide should be kept in mind in interpreting results.

Variations in the reaction of the urine have been compared with the results of fractional gastric analyses. The average values showed that definite changes in the reaction of the urine, commonly known as the alkaline tide, were present in specimens from patients who secreted more than minimal amounts of hydrochloric acid in the gastric juice, but that no such changes were found when the stomach contents contained little or no acid. A method for determining whether or not a tide is present in a given case has been proposed, and it has been shown that, as judged by it, the presence or absence of a tide agreed with the results of fractional gastric analysis in about 80 per cent of the cases studied. The presence or absence of the tide cannot be taken as the final proof of the presence or absence of hydrochloric acid in the stomach, because the results of the two analyses do not agree perfectly, because an absence of the tide can be demonstrated in cases in which acid is present in greatly reduced amounts, and because the urine acidity is influenced by

18 Bell, J. R., and MacAdam, W. The Variations in Gastric Secretion of the Normal Individual, *Am. J. M. Sc.* **167** 520 (April) 1924. Friedenwald, Gant and Morrison (Footnote 10).

19 Rabinowitch, I. M. The Origin of Urinary Ammonia, second paper, *Arch. Int. Med.* **33** 394 (March) 1924.

20 Stieglitz, E. J. Histologic Hydrogen Ion Studies of the Kidney, *Arch. Int. Med.* **33** 483 (April) 1924.

some factors, such as changes in the respiratory rate and, possibly, kidney damage, which are not connected with the gastric secretion. The method should prove useful in studying gastric cases on which direct analyses cannot be obtained, and in checking results showing low concentrations of acid in the gastric juice, for the agreement between the two methods is good if not perfect, and the factors which influence the reaction of the urine are very different from those which sometimes render the values obtained in fractional gastric analysis uncertain.

SIMULTANEOUS DETERMINATIONS OF GASTRIC ACIDITY AND THE ALKALINE TIDE IN URINE*

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In the preceding paper, it has been shown that an alkaline tide can be demonstrated in most cases in which hydrochloric acid is secreted by the stomach, but is not present in cases of achlorhydria or in subjects who secrete very little acid. The present paper is a brief report of a few experiments made to determine how much acid the stomach must secrete to cause the changes in the urine.

In the experiments reported in the preceding article, gastric analyses and alkaline tide determinations were not made simultaneously. There are obvious objections to comparing directly results so obtained. In some cases, the gastric curves found on the same subject resemble each other closely,¹ in others, this is not true.² In some instances, variations in the acidity in different parts of the stomach³ may account for the findings, for the tube may rest in different parts of the organ, but even when the gastric juice is thoroughly mixed before the specimens are taken marked variations in the curves are sometimes, though rarely, found.⁴ It seems probable that nausea and psychic states, such as fear and rage, which have an influence on the gastric secretion of man,⁵ may sometimes cause the discrepancies.

In carrying out simultaneous determinations, other difficulties were encountered which rendered the interpretation of the results uncertain. It has been shown in an earlier article⁶ that tides are sometimes practically absent after meals high in carbohydrate, to study these changes.

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1 Bennett, T. I., and Ryle, J. A. Studies on Gastric Secretion, V, A Study of Normal Gastric Secretion Based on the Investigation of One Hundred Healthy Men by Means of the Fractional Method of Gastric Analysis, Guy's Hosp Rep **71** 286 (July) 1921.

2 Bell, J. R., and MacAdam, W. The Variations in Gastric Secretion of the Normal Individual, Am J M Sc **167** 520 (April) 1924.

3 Gorham, F. D. Variations of Acid Concentration in Different Parts of the Gastric Chyme and Its Relation to Clinical Methods of Gastric Analysis, Arch Int Med **27** 434 (April) 1921.

4 Friedenwald, J. G., Gantt, N. H., and Morrison, T. H. Studies in Fractional Analysis, Ann Clin Med **2** 292 (March) 1924.

5 Ryle, G. A. Studies in Gastric Secretion IV, Some Individual Experiments with the Gastric Tube, Guy's Hosp Rep **71** 158 (April) 1921. Bennett, T. I., and Venables, J. F. The Effect of the Emotions on Gastric Secretion and Motility in the Human Being, Brit M J **2** 662 (Oct 30) 1920.

6 Hubbard, R. S., Munford, S. A., and Allen, E. G. Gastric Secretion and the "Alkaline Tide" in Urine, Am J Physiol **68** 207 (April) 1924.

in the reaction of urine, it is therefore necessary to use meals containing various foodstuffs. Such meals often give curves, when fractional analyses are carried out, which are difficult to interpret. If an attempt is made to find out how much acid is needed to cause a change in the reaction of the urine, it is necessary to know not only the concentration of acid in the gastric juice but also how much of it is formed in a given time. This cannot be determined without removing the entire gastric contents at frequent intervals. Such a procedure would make a study of the changes in the reaction of the urine meaningless, for the acid would not be absorbed in the intestinal tract, and no tide which even approximated those normally present could be obtained. It is even uncertain whether tides found when small specimens are withdrawn can properly

TABLE 1.—*Breakfasts*

Name	Sign	Foodstuffs	Foods	Grams
Gastric test meal	T	2 slices of bread soaked in water	Carbohydrate	33
			Protein	6
High protein	P	100 gm cottage cheese, 105 gm steak, albumin of 5 boiled eggs, 228 cc of water	Carbohydrate	4
			Protein	63
			Fat	18
Standard	S	60 gm toast, 13 gm butter, 50 gm egg, 200 cc milk, 200 cc water	Carbohydrate	42
			Protein	19
			Fat	26
High carbohydrate 1	C 1	110 gm pitted dates, 25 gm shredded wheat, 7 gm sugar, 356 cc water	Carbohydrate	106
			Protein	4
			Fat	3
High carbohydrate 2	C 2	88 gm pitted dates, 25 gm shredded wheat, 5 gm sugar, 468 cc water	Carbohydrate	75
			Protein	3
			Fat	3
High carbohydrate 3	C 3	25 gm shredded wheat, 24 gm sugar, 60 gm bread, 250 cc water	Carbohydrate	75
			Protein	9
			Fat	1
High carbohydrate 4	C 4	25 gm shredded wheat, 103 gm stewed prunes, 3 gm sugar, 430 cc water	Carbohydrate	56
			Protein	4
			Fat	0.5

be considered normal. In spite of these objections to the interpretation of results, it has seemed worth while to carry through a few experiments to show approximately what concentration of acid corresponds with the presence of a tide.

In these experiments, a Rehfuss tube was passed, and a specimen of gastric residuum removed. Different meals were fed, and specimens withdrawn at intervals of half an hour throughout the experiment.⁷ The alkaline tide was determined by the method described in the preceding article. The meals used, with the abbreviations by which they have been designated in the discussion, are given in Table 1.

⁷ Rehfuss, M. E. A New Method of Gastric Testing, with a Description of a Method for the Fractional Testing of the Gastric Juice, Am J M Sc 147 848, 1914. Rehfuss, M. E., Bergelm, O., and Hawk, P. B. Gastro-Intestinal Studies, II, The Fractional Study of the Gastric Juice with a Description of Normal and Pathologic Curves, J A M A 63 909, 1914.

In Table 2, all the gastric analyses obtained on one of us, E G A, a normal man doing light laboratory work, are given. After the test meal, the relationship between the hydrochloric acid and total acid was normal, but when other breakfasts were fed, the total acid concentration was very high compared with the amount of hydrochloric acid present. The difference was most marked when the breakfasts contained large amounts of carbohydrate. This finding may be due to a partial neutralization of hydrochloric acid by the products of digestion, to the presence of acid products formed from the food in the course

TABLE 2.—*Gastric Analyses on Normal Subject, E G A, After Different Meals*

Meal Time	T		S		P		C 1		C 2		C 4		
	Hydro- chloric Acid, C c	Total, C c											
	Residuum	After	0	13	0	0	0	11	0	23	0	8	30
0 20							0	53					72
0 30	6	18	0	42	0	80	0	88	3	21	Trace	61	
1 00	20	53	3	81	Trace	55	0	110	5	31	0	80	
1 30	36	54	23	87	17	91	0	71	21	50	14	69	
2 00	35	51	22	91	30	68	18	78	30	54	24	68	
2 30			38	93	58	102	0	86	15	34	39	64	
3 00			55	95	60	127	0	12	11	26	32	48	
3 30			69	91	70	130	0	7	30	46	Trace	48	
4 00			56	68	60	87			6	8			
4 30			0	12	41	67							
5 00					35	62							

TABLE 3.—*Gastric Analyses on Patient with Hypochlorhydria*

Meal	T		S	
	Hydrochloric Acid, C c	Total, C c	Hydrochloric Acid, C c	Total, C c
	None obtained		0 0	50
Residuum	0 0	40		
After meal	0 45	60		
	1 00	70	0 0	34 0
	1 15	20	20 0	
	1 30		0 0	27 0
	1 45	32 0	0 0	23 0
	2 00		0 0	
	2 15	32 0	0 0	30 0
	2 30		0 0	
	2 45	15 0	0 0	40 0
	3 00		0 0	
	3 30		0 0	28 0

of digestion, or to both causes. In Table 3, results on another subject are given which make it seem probable that these increases in total acid are due in part at least to the neutralization of hydrochloric acid, for an achlorhydria was found when the standard breakfast was fed, while after the gastric test meal hydrochloric acid was present, although only in small amounts. If this explanation is correct it is not possible to determine in a satisfactory manner the relationship between the concentration of acid in the gastric secretion and the alkaline tide, for a secretion of hydrochloric acid by the stomach, whether it is or is not neutralized must cause the changes in the blood which produce the alkaline tide.⁸

⁸ Bennett, T I., and Dodds, E C. The Gastric and Respiratory Response to Meals, Brit J Exper Path 2 58 (April) 1921.

TABLE 4.—Results on Subject, E. G. A.

		Fractional Gastric Analysis			Alkaline Tide	
Meal T	Time, A. M.	Hydrochloric Acid		Total C c	Hour, A. M.	Reaction <i>p</i> _H
		Tenth C c	Normal per 100 C c			
	9 20 (residuum)	0 0		13 0	7 20-8 20	5 6
	10 05	6 0		18 0	8 20-9 20	5 6
	10 50	20 0		53 0	9 20-10 20	5 8
	11 10	36 0		54 0		
	11 45	35 0		51 0	10 20-11 20	5 7
					11 20-12 20	5 8
S	8 35 (residuum)	0 0		6 0	7 00-8 00	5 7
	9 05	0 0		42 0	8 00-9 00	5 8
	9 35	3 0		81 0		
	10 05	23 0		87 0	9 00-10 00	6 4
	10 35	22 0		91 0		
	11 05	38 0		93 0	10 00-11 00	6 5
	11 35	55 0		95 0		
	12 05	69 0		91 0	11 00-12 00	6 0
	12 35	56 0		68 0		
					12 00-1 00	5 6
P	8 50 (residuum)	0 0		11 0	7 30-8 30	5 7
	9 10	0 0		53 0		
	9 20	0 0		80 0		
	9 50	Trace		55 0	8 30-9 30	5 7
	10 20	17 0		91 0		
	10 50	30 0		68 0	9 30-10 30	6 6
	11 20	58 0		102 0		
	11 50	60 0		127 0	10 30-11 30	7 0
	12 20	70 0		130 0		
	12 50	60 0		87 0	11 30-12 30	6 5
	1 20	41 0		67 0		
	1 50	35 0		62 0	12 30-1 30	5 4
					1 30-2 00	5 0
C 4	8 40 (residuum)	30 0		72 0	7 45-8 20	5 5
	9 10	Trace		61 0		
	9 45	0 0		80 0	8 20-9 20	5 6
	10 10	14 0		69 0		
	10 40	24 0		68 0	9 20-10 20	5 8
	11 10	39 0		64 0		
	11 40	32 0		48 0	10 20-11 20	6 5
	12 10	Trace		48 0		
					11 20-12 20	5 6
C 3	8 25 (residuum)	0 0		8 0	7 00-8 10	5 7
	9 15	3 0		21 0	8 10-9 10	5 8
	9 45	5 0		31 0		
	10 15	21 0		50 0	9 10-10 10	6 4
	10 45	30 0		54 0		
	11 15	15 0		34 0	10 10-11 10	6 5
	11 45	11 0		26 0		
	12 15	30 0		46 0	11 10-12 10	6 0
	12 45	0 0		8 0		
					12 10-1 10	5 6

TABLE 4—Results on Subject, E G A—(Continued)

Meal	Time, A M	Fractional Gastric Analysis			Alkaline Tide	
		H ₃ hydrochloric Acid Tenth Normal per 100 C c	Total C c	Hour, A M	Reaction, pH	
C 1	8 40 (residuum)	0 0	23 0	7 30- 8 30	5 4	
	9 10	0 0	68 0			
	9 40	0 0	110 0	8 30- 9 30	5 4	
	10 10	0 0	71 0			
	10 40	18 0	78 0	9 30-10 30	5 3	
	11 10	0 0	36 0			
	11 40	0 0	12 0	10 30-11 30	5 0	
	12 05	0 0	7 0			
				11 30-12 30	5 2	

The meals were fed immediately after the residual specimens were obtained.

In Table 4, the results of simultaneous studies on the urine and gastric contents of subject E G A are given. In the alkaline tides from him, when the tube was not in the stomach, as have been previously described,⁶ it was found that the intensity of the tide varied with the meals fed in much the same manner as did the secretion of hydrochloric acid after similar meals reported by others.⁹ The results reported here conform to the figures previously obtained. The meal highest in protein caused the highest secretion of acid in the gastric juice and the most marked tide found in any of the experiments. A similar meal caused the most marked tide in the previous study. The meal highest in carbohydrate was followed by a secretion of very small amounts of acid and no tide, in the previous study, no tide followed the ingestion of the meal highest in carbohydrate used. Concentrations of acid and intensities of tides found after other meals were intermediate, and varied approximately as the concentrations of protein in the meals, in the results presented in the other paper, the depth of the tide after the standard breakfast was intermediate between those which followed meals higher in protein and in carbohydrate. These results furnish strong confirmation of the theory that the secretion of hydrochloric acid determines the presence and intensity of the alkaline tide.

It is difficult to decide from the results the amount of hydrochloric acid which must be secreted to produce a tide. A concentration of 35 c c of tenth normal hydrochloric acid and 54 c c of tenth normal total acid after the gastric test meal, Experiment T, was not accompanied by a tide, while 24 c c of hydrochloric acid and 68 c c of total acid (Experiment C 4) and 21 c c of hydrochloric acid and 50 c c of total acid (Experiment C 3) did cause tides. We feel that there are enough unavoidable factors, such as variations in the amount of gastric juice

⁹ Rehfuss, M. E., and Hawk, P. B. A Consideration of the Gastric Test Meal from Experimental Data, J. A. M. A. 75: 449 (Aug. 14) 1920.

secreted, variations in concentration of hydrochloric acid in different parts of the stomach, and partial neutralization of hydrochloric acid secreted, to account for these discrepancies.

In Table 5, data obtained in a somewhat different way are reported. The same subject took the meals indicated. Tides developed, and half way through each experiment a tube was swallowed and a sample of gastric juice obtained. Thirty-five cubic centimeters of hydrochloric acid and 47 cc of total acid in one experiment, and 44 cc of hydrochloric acid and 106 cc of total acid in the other caused tides. In the second result, the large amounts of total acid found make it seem probable that a part of the hydrochloric acid produced by the stomach had been neutralized by products of digestion, and therefore it does not

TABLE 5.—*Single Specimen Gastric Analysis and Tides in E G A*

Meal	Time, A M	Single Specimen Gastric Study		Alkaline Tide	
		Hydrochloric Acid Tenth Normal per Cc	Total Cc	Hour, A M	Reaction, pH
O 2				7 32-8 37	5 6
				8 37-9 37	5 6
				9 37-10 37	6 4
	10 43	35 0	47 0	10 37-11 37	6 7
				11 37-12 37	5 6
S				7 20-8 30	5 6
				8 30-9 30	5 7
				9 30-10 30	6 9
	10 45	44 0	106 0	10 30-11 30	6 6
				11 30-12 30	5 7

The tube was swallowed just before the gastric specimen was obtained. The meals, as indicated, were taken about half an hour after the first urine specimen was voided.

seem unreasonable that a tide should be found, but the figures in the first experiment are almost identical with those found after the gastric test meal (Experiment T, Table 4) when no tide developed. We are inclined to attribute the discrepancy to differences in the total amount of gastric juice secreted, although variations in the acidity of different parts of the stomach cannot be excluded as a cause.

In Table 6, results on three other subjects who took the standard breakfast are given. In Case 1, large amounts of acid were present in the gastric juice, and a marked tide developed. Case 2 showed no hydrochloric acid and but little total acid in the gastric juice, and an absence of a tide in the urine specimens. Case 3 also showed an achlorhydria, but it was associated with somewhat larger amounts of total acid and a well marked alkaline tide. A gastric analysis after the usual test meal was carried out on the patient, and some hydrochloric acid found, as shown in Table 3. Qualitatively these results agree well with the theory of an association between the secretion of the gastric juice and the occurrence of the alkaline tide but quantitatively, they are

hard to interpret, for a tide developed in Case 3 when the stomach contained no hydrochloric acid and only 40 c.c. of tenth normal total acid in 100 c.c. In this last case, some hydrochloric acid was probably neutralized, for gastric analysis after the usual test meal showed hydrochloric acid present, but this does not account adequately for the discrepancy between the gastric and urine findings. It seems to us that the samples drawn, in this case, do not accurately represent conditions in the stomach as a whole.

The experiments described above furnish throughout strong evidence in favor of the theory that the secretion of acid by the stomach causes the alkaline tide in urine, but owing to difficulties in determining the actual

TABLE 6.—*Results on Three Patients*

Number	Time, A.M.	Fractional Gastric Analysis		Alkaline Tide		
		Hydrochloric Acid C.c.	Total Tenth Normal per 100 C.c.	Hour, A.M.	Reaction, pH	
					7 00-8 00	5 8
1	8 30 (residuum)	0 0	15 0			
	9 30	0 0	37 5			
	10 00	0 0	61 0			
	10 30	6 0	83 0	8 00-10 00		7 2
	11 00	10 0	87 0	10 00-11 00		8 0
	11 30	67 5	98 5			
	12 00	75 0	95 0	11 00-12 00		8 0
2	8 30 (residuum)	0 0	3 0	7 00-8 00		7 7
	9 30	0 0	22 0	8 00-9 00		6 9
	10 45	0 0	19 0	9 00-10 00		6 2
	11 45	0 0	22 0	10 00-11 00		6 6
				11 00-12 00		6 7
3	8 30 (residuum)	0 0	5 0	7 00-8 00		5 9
	9 30	0 0	34 0	8 00-9 00		5 9
	10 00	0 0	27 0	9 00-10 00		5 7
	10 30	0 0	23 0			
	11 00	0 0	30 0	10 00-11 00		6 4
	11 35	0 0	40 0			
	12 00	0 0	28 0	11 00-12 00		6 8

The standard breakfast, S, was fed to each patient between 8 30 and 9 1 m.

amount of hydrochloric acid secreted by the stomach at any given time, in deciding how much of the hydrochloric acid produced has been neutralized by products of digestion, and in making sure that the results of an analysis represent conditions in the whole stomach, they furnish only a little help in studying how much acid must be secreted by the stomach to produce a tide. It is certain that some acid may be present in the stomach without causing these changes in the urine, and in some cases such amounts as occur in normal gastric juice may be present, at least in part of the stomach, without producing these changes in the urine. When a tide is present, therefore it seems probable that the

presence in the stomach of more hydrochloric acid than is usually secreted in hypochlorhydria must be assumed, in most cases. The patient may nevertheless, have this condition, for the meals used in studying the tide lead to a production of higher concentrations of acid than do those used in the usual gastric tests, and it is on the response of the stomach to gastric test meals that the definitions of hypochlorhydria and hyperchlorhydria are based.

ATYPICAL CASE OF SPLENOMEGLY *

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The case of splenomegaly to be reported shows such an atypical course that we feel that it will be justifiable to report it now, while the patient is yet under observation

REPORT OF CASE

A woman, aged 60 with a negative family history, had an attack of typhoid fever, at the age of 10. At 29, during the seventh month of pregnancy, she suffered from eclampsia, with miscarriage. The next year, she had a second miscarriage, in the eighth month of gestation. For the following five years, she felt very weak, and gave birth to a delicate child. For the next six years, there was some improvement, during which time she gave birth to two healthy children. At 41, during her sixth pregnancy there was a recurrence of the weakness, with constant pain in the region of the spleen. A diagnosis of enlarged spleen was made and extirpation of the spleen advised, but it was refused by the patient. Since that time, her complaints have been the same—weakness, nervousness, palpitation of the heart, pain in the arms and legs, and pain in the abdomen, first on the left side but for the last few years on the right side, in the region of the liver. The bowels and kidneys were normal. There was no bleeding from any place.

Physical examination made in July, 1914 revealed that the spleen was enlarged and hard, extending to the umbilicus. The lymph glands were not enlarged. The liver was nonpalpable. The blood count was erythrocytes, 3,008,000, leukocytes, 8,300. The differential count was polymorphonuclears, 64 per cent, small lymphocytes, 17 per cent, large lymphocytes, 14 per cent, and transitionals, 5 per cent. Myelocytes were absent.

Examination made in August 1915, gave the following findings. The spleen extended almost to the midline, and below the umbilicus to the crest of the left ilium, the edge was sharp, the notch palpable. It was not tender. The liver was not palpable. The Wassermann reaction was negative. Erythrocytes totaled 3,616,000 and leukocytes, 5,600, the differential count was normal, there were no abnormal cells found.

Examination in December, 1923, gave the following results. The spleen extended to the midline and reached into the pelvis. It was hard, smooth and not painful. The lymph glands were not enlarged. The liver extended down to the umbilicus, was hard, smooth and rather tender.

The last examination, in May, 1924, gave the following findings. The patient appeared poorly nourished. The skin was brown, smooth and dry. Some of the cervical, inguinal and axillary lymph glands were slightly enlarged. They were solid, freely movable, smooth and not tender. The throat and mouth were negative. The heart was normal, except for a slight, functional systolic murmur. The lungs were normal. Neither kidney was palpable. There was no jaundice, no dilated veins, and no evidence of ascites. The spleen was greatly enlarged, to the upper margin at the eighth rib, extending to the umbilicus and continuing in a downward direction, 3 inches (7.6 cm) to the right of the midline, and

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into the pelvis 3 inches (7.6 cm) below the umbilicus. The notch was plainly felt in the region of the umbilicus. The surface was smooth, firm, and not tender to pressure. The spleen was movable. The upper border of the liver was at the level of the sixth rib, the lower border at the level of the umbilicus. The surface was smooth, firm and tender to pressure. The edge was sharp. The genitalia, extremities and reflexes were normal.

During the ten years that the patient has been under our observation, a number of careful blood studies have been made, showing only secondary anemia with leukopenia. The first changes occurred Oct 15, 1923, when the blood findings were as follows: Erythrocytes, 3,584,000, hemoglobin, 55 per cent (Sahli), and leukocytes 4,200. The differential count showed polymorphonuclears, 38 per cent, large lymphocytes, 4 per cent, small lymphocytes, 8 per cent, transitional, 7 per cent, eosinophils, 3 per cent, basophils, 2 per cent, neutrophilic myelocytes, 25 per cent, eosinophilic myelocytes, 4 per cent, basophilic myelocytes, 2 per cent, myeloblasts, 2 per cent, and normoblasts, 5 per cent. The red cells showed variation in size and shape, with rare polychromatophilic cells and stippling. The platelets were increased in number, and were frequently abnormally large. The numbers of leukocytes were increasing until, May 5, 1924, they reached 38,600. The white count was irregular, with periods of spontaneous remissions.

December 22, the general condition of the patient was unchanged and she was able to perform her house duties. The spleen was not more enlarged than it was in May. The blood counts constantly showed secondary anemia, a white cell count of 25,000, myelocytes and normoblasts.

COMMENT

The striking feature of this case is its long continued course. The progress of the disease can be divided into three periods (1) splenic, (2) hepatic and (3) myeloid stage.

Enlargement of the spleen was diagnosed nineteen years ago. Since typhoid fever in childhood, the patient had felt weak and nervous. The symptoms became more pronounced after eclampsia, thirty years ago. It is possible that the spleen, enlarged during typhoid fever, never returned to its normal size, rendering it more susceptible to injury during eclampsia.

Enlargement of the liver was absent nine years ago. The blood pictures, in the splenic and hepatic stages, show only signs of anemia and leukopenia, which are common findings in diseases of the spleen, such as neoplastic growths.

The myeloid stage was initiated during October, 1923. It was characterized by definite changes in the bone marrow, manifested by typical myeloid changes in the blood.

It is well known that the spleen, liver and bone marrow are interrelated in their action. It is probable that the normal regulatory action of the spleen over the bone marrow was altered in such a manner as to cause an abnormal depression of the activity of the bone marrow without marked alteration of its character, as is evidenced in the chronic anemia and leukopenia, and by enlargement of the spleen and liver. In the

myelogenous stage there is hyperactivity of the bone marrow, giving rise to increased leukocyte count, and appearance of nucleated erythrocytes, myelocytes and blood platelets. The hyperactivity of the bone marrow may represent periods of remission when the bone marrow is able to overcome its depression of function, or may indicate that the spleen is affected to such a degree that the bone marrow is forced to increased activity, as is often seen after the removal of the spleen. It cannot yet be definitely stated whether the myelogenous stage is a remission or an indication of progression of the disease to a terminal stage. Clinical findings make the latter more probable.

The clinical course and our observation make very improbable the possibility that a chronic splenomegaly of very long duration with absolute absence of pathologic cells in blood changed now to another new disease—subleukemic myelosis (splenomyelogenous leukemia). Here the myeloid stage is only a biologic reaction of the bone marrow.

In Banti's splenomegaly, the tendency to hemorrhages, especially from the stomach and the rectum, is very prominent. The blood picture always shows secondary anemia and leukopenia. The third terminal stage of the disease shows symptoms simulating atrophic cirrhosis of the liver, ascites being the principal one.

Although a review of the literature of splenomegaly does not yield a description of a case of splenomegaly with the myelogenous stage, still it seems logical to expect such an involvement, in view of the close interdependence of the spleen and bone marrow.

The etiology of such diseases is still obscure. Infectious diseases, especially those which, like typhoid fever, seriously affect the spleen, are supposed to be predisposing. The effect of disturbances of the inner secretions is still unknown. The physiology of the correlations between the spleen and the bone marrow is not well enough established to make clear the etiology of such cases.

Since the etiology is obscure, the treatment, either medical or surgical, is not satisfactory in such cases. The patient was treated symptomatically for a long period, but without results. Roentgen-ray treatment also was not effective. Treatment has been discontinued, and the patient remains in the same condition as before.

SUMMARY

A woman, aged 60, who had had typhoid fever at the age of 10, and eclampsia at 31, nineteen years ago received a diagnosis of enlarged spleen. The present findings were a greatly enlarged spleen and liver. The blood findings were anemia and leukopenia until a few months ago,

when leukocytosis, with myeloid changes, appeared. The course of the disease was divided into the three stages, splenic, hepatic and myeloid, the first stage lasted over a period of twenty years, the second over a period of a few years, and the last has been in evidence for nine months.

The spleen, liver and bone marrow are interrelated in their function. Our case represents a pathologic correlation of these three, while usually only involvement of the spleen and liver is seen.

THE MECHANISM OF REACTION OF NON-SPECIFIC PROTEIN AGENTS IN THE TREATMENT OF DISEASE

I THE INFLUENCE OF VARIOUS AGENTS ON TEMPERATURE AND LEUKOCYTE COUNTS IN NORMAL PERSONS AND IN RABBITS *

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Just what portion of a protein stimulates the thermoregulatory center in nonspecific protein therapy is still an open subject for investigation, likewise, the degree of therapeutic activity to be ascribed to fever production is a subject of speculation.

Luke¹ believes that temperatures per se are not damaging factors in infections, for if in infectious diseases the temperature is artificially raised, the disease is seemingly favorably influenced. Antibodies that had gradually disappeared after an infection, or following immunization artificially produced, were again found in the serum after any procedure that increased the body temperature, whether by increasing the external temperature, by influencing the thermal center of the brain or by injecting pyrogenic drugs. It tends to show that hyperthermia has a direct stimulating effect on the previously formed antibodies, causing the latter to mobilize freely and thus, in turn, to influence the disease processes.

On the other hand, Uddgren,² as a result of extensive studies with milk injections, was led to believe that hyperthermia alone could not be responsible for the clinical improvements observed. Working on eye diseases, she found that with sterile milk the reaction of the patients was mild but the therapeutic results were just as good as, if not better than, when market milk was used, which gave a severe febrile reaction.

The reactive temperature following a single injection of foreign protein, varying from a mere suggestion of febrile disturbance to a decided rise of from 1 to 2 degrees Fahrenheit, or even more, has been recorded.³ Most observers seem to agree, however, that together with

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1 Quoted from Petersen, W F Protein Therapy and Nonspecific Resistance, New York, Macmillan Company, 1922, p 90

2 Uddgren, G Milchinjection in der Ophthalmologie, Stockholm, 1918, quoted from Petersen, W F Protein Therapy and Nonspecific Resistance, New York, Macmillan Company, 1922, p 90

3 Barkan, O, and Nelson, R F The Active Agent in Milk Injection, J A M A 82 190 (Jan 19) 1924

the desired therapeutic results following protein treatment a rise of temperature to some extent is usually expected

Now, let us turn for a moment into nonspecific response of peripheral blood leukocytes. The fact that leukocytes do not constitute the main source from which to derive the defensive factors in immune processes has now been fairly well established. This does not deny in the least, however, the important rôle played by them as phagocytes, especially by neutrophilic polymorphonuclears and by large lymphocytes, in combating the infections.

Furthermore, leukocytes may possibly liberate endolysins, which exercise, as do the bacteriolysins, bactericidal activities in the blood.⁴ They also may elaborate proteolytic and peptolytic enzymes⁵ (leuko-proteases) helping to digest and to eliminate any foreign proteins invading the system.

The rôle of leukocytes, in immune processes, has been extensively studied, though by no means is it an exhausted field of research. The works of Metchnikoff and his pupils on phagocytosis, those of Schattenfroh, Petterson, Hiss and others on bactericidal activities of leukocytes, and those of Petersen and others on leukocytic enzymes have well covered these fields. It will be unnecessary to enter here into these subjects which are so well known and of which the literatures are so accessible. The discussions in Kolmer's "Infection, Immunology and Biologic Therapy" give a comprehensive idea of these subjects.

With the introduction of nonspecific protein therapy, various agents, such as horse serum, milk, peptone, vaccines of various kinds, yeasts, crotalín and distilled water, have been employed. Leukocytic responses have been carefully studied by Lange,⁶ Scully,⁷ Gow,⁸ Spangler,⁹ Barkan³ and others. The total leukocyte counts made after one single injection of protein, varying from 15,000 to 30,000, have been observed. In most cases, the reactive leukocytosis that follows is of myeloid types, that is, of neutrophilic polymorphonuclears, large mononuclears and transitional types. Eosinophils also are increased at times. The lymphatic apparatus is relatively passive.

⁴ Manwaring, W H. The Nature of the Bactericidal Substance in Leukocytic Extract, *J Exper Med* **16** 250, 1912.

⁵ Petersen, W F. The Ferment Antiferment Balance and Its Relation to Therapeusis, *Arch Int Med* **20** 515 (Oct) 1917.

⁶ Lange, F. Experimentelle Untersuchungen über das Verhalten der Leukocyten nach Injektion von Bakterienextrakten, *Deutsch Arch f klin Med* **94** 552, 1908.

⁷ Scully, F T. The Reaction After Intravenous Injections of Foreign Proteins, *J A M A* **69** 20 (July 7) 1917.

⁸ Gow, A E. Concerning Protein Shock in Intravenous Vaccine Therapy, *St Barth Hosp J* **25** 75, 1918-1919.

⁹ Spangler, R H. Eosinophilia Produced by Hypodermic Injections of Crotalín Solution, *New York M J*, Oct 4, 1913.

Leukocytic reactions, as well as temperature responses, depend, of course, on types of infections, synchronous conditions of the patients and finally, but not last, on the dosage and chemical nature of the particular protein agents employed, besides individual reactive differences.

In this work, eight agents were used, viz., distilled water, auto-serum, horse serum, certified milk, market milk, crotalins, peptone and typhoid vaccine. By employing accepted doses and using normal subjects and rabbits, in these experiments, a favorable approach has seemed to have been made to the study of the relative values of these protein agents used in producing nonspecific biologic reactions.

PURPOSE OF INVESTIGATION

In view of the growing practical importance of protein therapy, particularly for the production of initial nonspecific resistance in diseases of bacterial origin, such as arthritis, acute or chronic, gonorrhea, typhoid fever and anthrax, the question of using the right protein agents for appropriate cases has offered a new field for research. In this work, a series of comparative studies were undertaken, in which various agents commonly employed in clinical and experimental work were used. Different biologic methods were employed.

There are, in these studies, four distinct objects in view:

- 1 To study comparatively the influence of various nonspecific protein agents on the reactive temperature.
- 2 To study comparatively the influence of various nonspecific protein agents on the mobilization of peripheral blood leukocytes.
- 3 To study comparatively the influence of various nonspecific protein agents on the mobilization of blood antibodies.
- 4 To study comparatively the influence of various nonspecific protein agents on the mobilization of blood enzymes.

The results of the first two of these studies concerning temperature and leukocytes are summarized in this paper, the results of those concerning blood antibodies and blood enzymes are given in two succeeding papers.

TECHNIC

All the agents employed, except the distilled water, were of some form of proteins.

- 1 Sterile distilled water.
- 2 Autoserum, separated from the blood of the same person or rabbit, after being placed for four hours in the refrigerator.
- 3 Normal horse serum, the stock serum, prepared by Mulford Laboratory for the use in therapeutic purposes.
- 4 Certified milk, with a bacterial count of not more than 10,000 per cubic centimeter. The milk was boiled at 100 degrees C for ten minutes.

5 Market milk, with a bacterial count of between 300,000 and 400,000 per cubic centimeter It was likewise boiled for ten minutes

6 Crotalim, in solution, kindly supplied by Dr Spangler of Philadelphia

7 One per cent peptone solution in saline, autoclaved for twenty minutes

8 Typhoid vaccine, suspended in saline solution, with 100,000,000 per cubic centimeter

All normal persons and rabbits were carefully weighed before the injection, and the amount of agent given was in proportion to their body weights, as follows

(a) Sterile distilled water 0.1 cc per kilogram of weight for human being, 1 cc per kilogram of weight for rabbit, given intravenously

(b) Autoseum 0.5 cc per kilogram of weight for human being and rabbit, given intravenously

(c) Sterile normal horse serum 0.2 cc per kilogram for human being and rabbit, given intravenously

(d) Certified milk 0.2 cc per kilogram of weight for human being and rabbit, given intramuscularly

(e) Market milk 0.2 cc per kilogram of weight for human being and rabbit, given intramuscularly

(f) Crotalim $\frac{1}{15}$ grain per kilogram of weight for human being, $\frac{1}{3}$ grain per kilogram of weight for rabbit, given hypodermically

(g) Peptone solution (1 per cent) 0.02 cc per kilogram of weight for human being and rabbit, intravenously

(h) Typhoid vaccine (100,000,000 per cubic centimeter) 0.2 cc per kilogram of weight for human being and rabbit, intravenously

Total leukocyte counts, differential counts and temperature observations were made just before, and four hours and twenty-four hours after the administration of the agents

To avoid the effect of food on the temperature and leukocytic fluctuation, all examinations were made in the early part of the morning before any food was given

A number of normal persons and rabbits also were similarly examined under the same condition for controls, and the composite results were obtained for comparison

RESULTS

The composite results of the experiments are expressed in the accompanying tables and Charts 1 to 5, and the study may be briefly summarized as follows

Influence on Temperature—Variations of febrile reactions in various individuals were not infrequently observed but in general, the adminis-

TABLE 1—*Influence of Various Agents on Temperature*

Agents	Times Examinations Were Made	Temperature in Degrees Fahrenheit			
		Rabbit	Human Being	Average	Mean Average*
Distilled water	Before injection	102.1	97.6	99.9	100.0
	4 hours after injection	103.0	98.8	100.9	101.0
	24 hours after injection	102.0	98.0	100.0	100.1
Autoserum	Before injection	101.9	97.0	99.5	100.0
	4 hours after injection	103.6	98.0	100.8	101.3
	24 hours after injection	101.5	97.0	99.3	99.8
Horse serum	Before injection	101.8	97.0	99.8	100.0
	4 hours after injection	102.1	98.4	100.3	100.5
	24 hours after injection	102.0	98.2	100.1	100.3
Certified milk	Before injection	102.1	99.2	100.2	100.0
	4 hours after injection	102.8	99.6	101.2	101.0
	24 hours after injection	101.4	99.1	100.3	100.1
Market milk	Before injection	102.2	98.6	100.4	100.0
	4 hours after injection	103.6	100.2	101.9	101.5
	24 hours after injection	103.0	100.0	101.5	101.1
Crotalins	Before injection	101.3	98.1	99.7	100.0
	4 hours after injection	102.6	98.6	100.6	100.9
	24 hours after injection	102.3	97.6	100.0	100.3
Peptone	Before injection	101.8	97.8	99.8	100.0
	4 hours after injection	103.3	100.2	101.8	102.0
	24 hours after injection	101.5	96.6	99.1	99.3
Typhoid vaccine	Before injection	102.0	98.6	100.3	100.0
	4 hours after injection	103.9	101.4	102.7	102.4
	24 hours after injection	101.7	100.2	101.0	100.7
Control	First examination	101.9	97.6	99.8	100.0
	Second examination	102.1	98.2	100.2	100.4
	Third examination	101.8	98.0	99.9	100.1

* Temperature taken before injection is arbitrarily set at 100 F Increase or decrease of two subsequent observations is then added to or subtracted from it

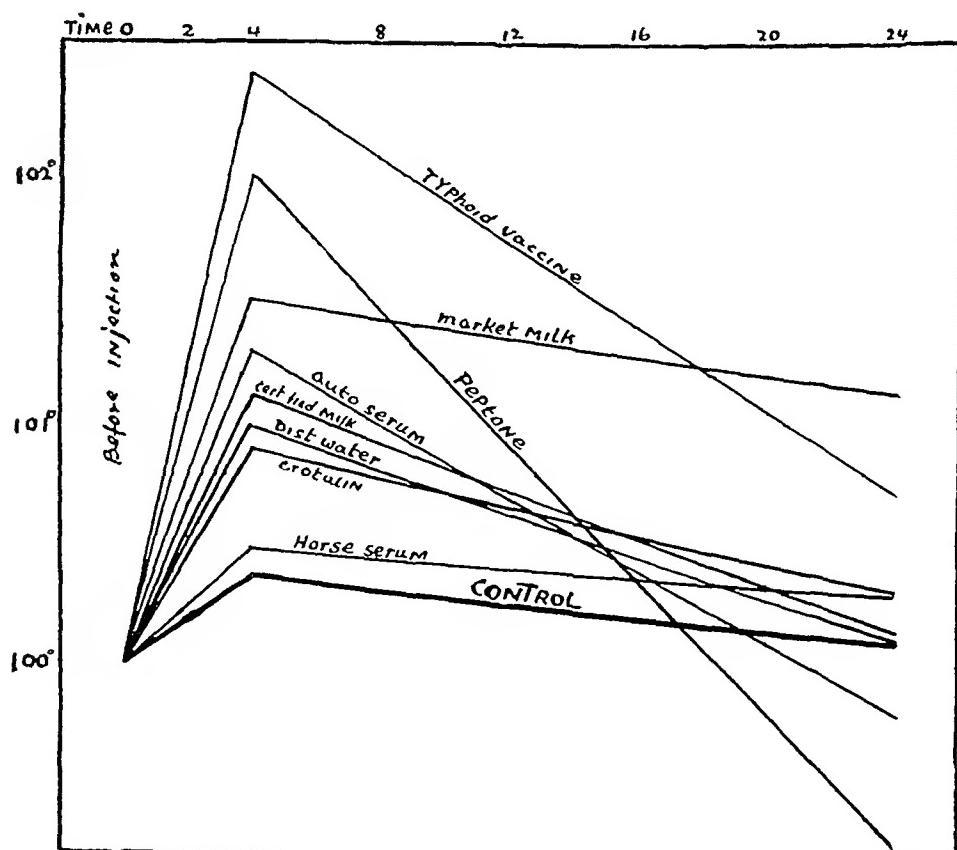


Chart 1—Composite results of influence of various agents on temperature

TABLE 2—Influence of Various Agents on Total Leukocyte Counts

Agents	Times Examinations Were Made	Number of Cells per C Mm. of Blood		
		Rabbit	Human Being	Average
Distilled water	Before injection	8,750	8,200	8,475
	4 hours after injection	7,600	7,600	7,125
	24 hours after injection	8,700	9,000	8,850
Autoserum	Before injection	8,900	8,200	8,550
	4 hours after injection	10,700	8,600	9,100
	24 hours after injection	9,500	8,400	8,400
Horse serum	Before injection	10,600	8,200	9,400
	4 hours after injection	13,400	7,600	10,500
	24 hours after injection	9,350	8,000	8,675
Certified milk	Before injection	4,200	8,320	6,260
	4 hours after injection	7,200	7,200	8,940
	24 hours after injection	3,200	8,210	7,430
Market milk	Before injection	7,770	8,850	8,310
	4 hours after injection	8,000	8,200	8,100
	24 hours after injection	13,100	12,000	12,550
Crotalins	Before injection	5,800	8,800	7,800
	4 hours after injection	7,000	8,200	7,800
	24 hours after injection	6,400	9,000	8,200
Peptone	Before injection	8,650	7,580	8,115
	4 hours after injection	8,200	7,320	7,760
	24 hours after injection	9,500	8,000	8,635
Typhoid vaccine	Before injection	9,200	10,400	9,800
	4 hours after injection	12,500	9,500	11,000
	24 hours after injection	15,800	9,000	12,400
Control	First examination	8,400	8,200	8,300
	Second examination	8,850	8,500	8,425
	Third examination	8,450	7,600	8,025

* The count taken before injection is arbitrarily set at 8,000. Increase or decrease of two subsequent counts is added to or subtracted from it.

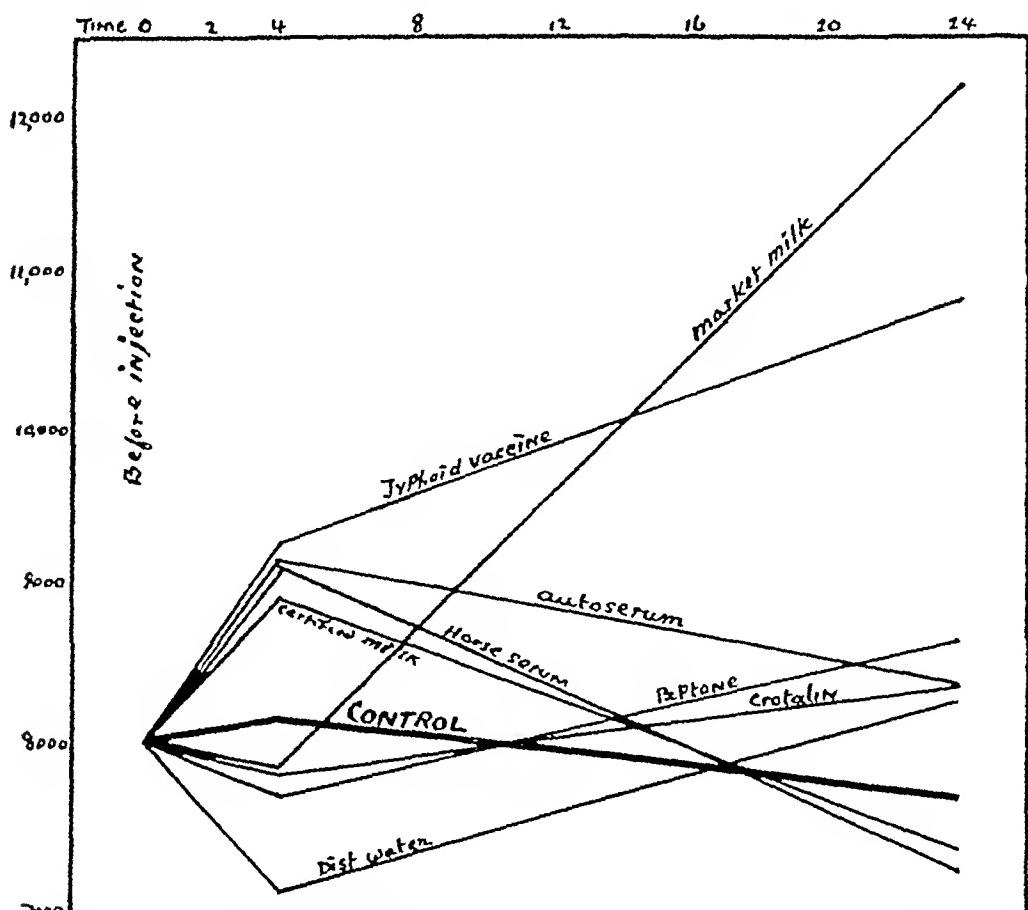


Chart 2—Composite results of influence of various agents on total leukocyte count

TABLE 3.—Influence of Various Agents on Neutrophilic Polymorphonuclears

Agents	Times Examinations Were Made	Number of Cells per C Mm. of Blood		
		Rabbit	Human Being	Average
Distilled water	Before injection	3,500	3,162	3,330
	4 hours after injection	4,100	3,509	3,510
	24 hours after injection	1,914	4,410	3,160
Autoserum	Before injection	2,848	5,740	4,290
	4 hours after injection	4,654	6,708	5,680
	24 hours after injection	1,805	5,712	3,760
Horse serum	Before injection	5,104	6,232	5,710
	4 hours after injection	4,422	5,258	4,840
	24 hours after injection	5,300	6,400	5,850
Certified milk	Before injection	1,092	5,229	3,160
	4 hours after injection	2,880	4,608	3,740
	24 hours after injection	256	5,576	2,920
Market milk	Before injection	3,108	5,487	4,300
	4 hours after injection	4,640	5,576	5,110
	24 hours after injection	6,701	8,880	7,790
Crotalins	Before injection	2,088	6,864	4,480
	4 hours after injection	2,275	5,904	4,090
	24 hours after injection	2,120	6,120	4,120
Peptone	Before injection	1,081	4,700	2,890
	4 hours after injection	4,838	5,856	5,350
	24 hours after injection	2,116	5,856	3,990
Typhoid vaccine	Before injection	2,668	5,840	4,250
	4 hours after injection	1,537	7,410	4,470
	24 hours after injection	7,979	7,380	7,680
Control	First examination	2,280	5,600	3,910
	Second examination	2,950	5,660	4,320
	Third examination	2,366	5,320	3,843

* The count taken before injection is arbitrarily set at 5,000. Increase or decrease of two subsequent counts is added or subtracted from it.

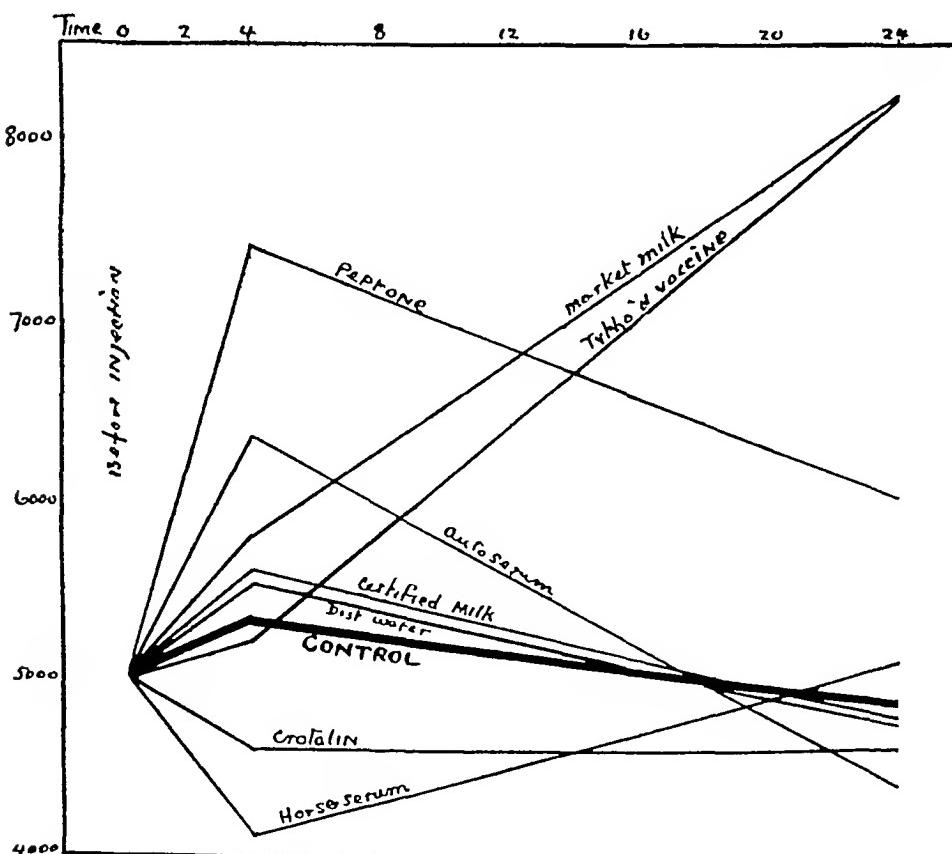


Chart 3.—Composite results of influence of various agents on neutrophilic polymorphonuclears

TABLE 4.—Influence of Various Agents on Lymphocytes

Agents	Times Examinations Were Made	Number of Cells per C Mm. of Blood		
		Rabbit	Human Being	Average
Distilled water	Before injection	4,080	3,200	3,640
	4 hours after injection	2,964	3,408	3,690
	24 hours after injection	4,000	4,032	4,160
Autoserum	Before injection	4,084	1,968	3,480
	4 hours after injection	3,243	1,032	3,140
	24 hours after injection	4,750	1,260	3,000
Horse serum	Before injection	4,604	2,640	3,620
	4 hours after injection	5,470	3,040	4,250
	24 hours after injection	3,114	1,960	2,540
Certified milk	Before injection	2,520	2,322	2,420
	4 hours after injection	1,870	1,440	1,600
	24 hours after injection	2,668	1,970	2,320
Market milk	Before injection	4,118	1,770	2,940
	4 hours after injection	2,480	1,470	1,980
	24 hours after injection	3,144	1,920	2,530
Crotalins	Before injection	2,726	1,040	2,330
	4 hours after injection	3,290	2,115	2,700
	24 hours after injection	2,584	1,800	2,190
Peptone	Before injection	4,022	1,820	3,220
	4 hours after injection	2,378	1,885	2,130
	24 hours after injection	3,725	1,200	2,460
Typhoid vaccine	Before injection	5,152	2,910	4,030
	4 hours after injection	4,250	2,000	3,160
	24 hours after injection	6,320	1,260	3,790
Control	First examination	4,260	1,840	3,050
	Second examination	4,330	1,990	3,160
	Third examination	4,807	1,900	3,250

* The count taken before injection is arbitrarily set at 2,000. Increase or decrease of two subsequent counts is added to or subtracted from it.

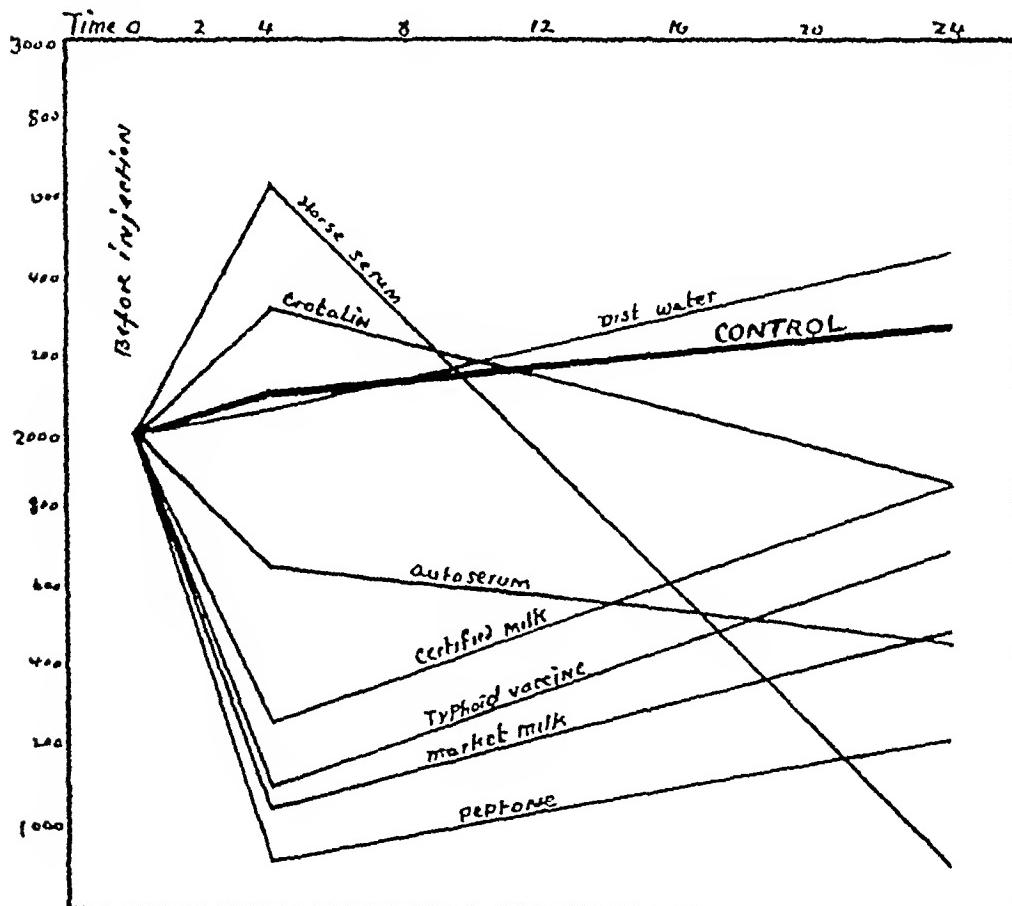


Chart 4—Composite results of influence of various agents on lymphocyte count

TABLE 5.—*Influence of Various Agents on Eosinophilic Polymorphonuclears*

Agents	Times Examinations Were Made	Number of Cells per C Mm of Blood		
		Rabbit	Human Being	Mean Average*
Distilled water	Before injection	250	124	200
	4 hours after injection	228	203	230
	24 hours after injection	535	70	310
Autoserum	Before injection	356	144	200
	4 hours after injection	856	63	410
	24 hours after injection	570	168	320
Horse serum	Before injection	212	120	200
	4 hours after injection	1,080	150	650
	24 hours after injection	186	40	140
Certified milk	Before injection	81	62	200
	4 hours after injection	440	36	370
	24 hours after injection	128	62	230
Market milk	Before injection	221	44	200
	4 hours after injection	640	116	400
	24 hours after injection	40	90	140
Crotalins	Before injection	116	9	200
	4 hours after injection	900	30	610
	24 hours after injection	65	50	200
Peptone	Before injection	256	33	200
	4 hours after injection	656	40	400
	24 hours after injection	240	60	700
Typhoid vaccine	Before injection	92	20	200
	4 hours after injection	250	26	280
	24 hours after injection	158	96	270
Control	First examination	160	40	200
	Second examination	476	20	248
	Third examination	280	90	285

* The count taken before injection is arbitrarily set at 200. Increase or decrease in two subsequent counts is added or subtracted from it.

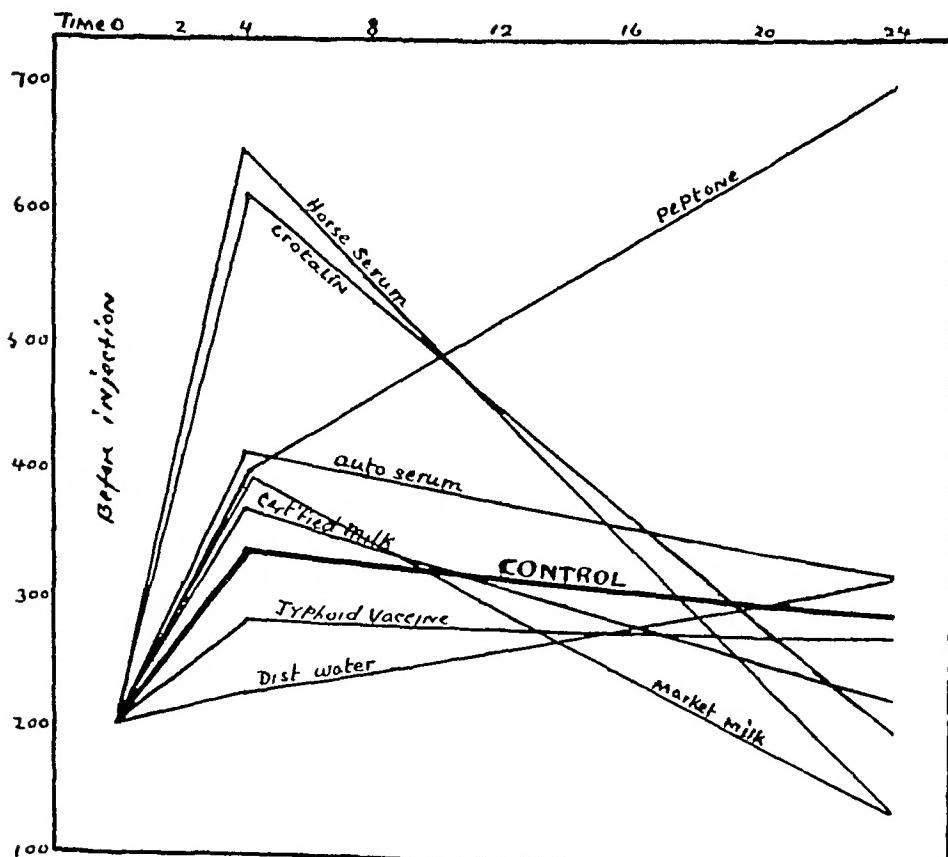


Chart 5.—Composite results of influence of various agents on eosinophilic polymorphonuclears

tration of all protein agents was usually followed, within four hours, by distinct elevation of temperature, with a return to normal or about normal in twenty-four hours. *Bacillus typhosus*, peptone and market milk gave the most prompt initial temperature reaction, while that produced by market milk seemed to persist longer than that of other agents (Table 1 and Chart 1).

Influence on Total Leukocyte Count—The leukocytic response was similar to temperature disturbances as far as the irregularities of the results are concerned. Market milk and *B. typhosus* were far more efficient in inducing a pronounced and persistent increase of total leukocyte count (Table 2 and Chart 2).

Influence on Neutrophilic Polymorphonucleas—Absolute increase of neutrophils apparently kept pace more closely with that of temperature than that of total counts. Market milk and typhoid vaccine produced, both in human being and rabbit, a most steady and persistent neutrophilic response, though peptone gave a prompter initial reaction (Table 3 and Chart 3).

Influence on Lymphocytes—Under the influence of horse serum, crotalins and distilled water, the lymphocytes were found slightly increased during the first stages of leukocytic reaction, while those administered with peptone, market milk, typhoid vaccine or certified milk showed a decided drop during the same period. The usual or normal level was generally recovered, however, in about twenty-four hours (Table 4, Chart 4).

Influence on Eosinophilic Polymorphonucleas—All rabbits invariably showed a slight increase after treatment. It was less so in the human beings. Peptone, horse serum and crotalins seemed to produce a decided eosinophilia.

CONCLUSIONS

1 All the agents used, including distilled water, autoserum, horse serum, certified milk, market milk, crotalins, peptone and typhoid vaccine, raise the temperature in normal persons or rabbits from 0.5 to 2.4 F., sometime within or about four hours after administration. The most decided rise is produced by typhoid vaccine, peptone, market milk and autoserum, named in the order of their effectiveness.

2 Peripheral blood leukocytes are more or less mobilized by all the agents used.

(a) Persistent leukocytosis is found after being treated with market milk or typhoid vaccine, named in the order of their effectiveness.

(b) Persistent increase of neutrophilic polymorphonucleas is found in those treated with market milk, typhoid vaccine and peptone.

- (c) Persistent lymphocytosis is found in those treated with distilled water and crotalins
- (d) Persistent eosinophilia is seen in those treated with peptone solution

TRANSIENT CHANGE IN THE AURICULOVENTRICULAR CONDITION FOLLOWING THE INJECTION OF HISTAMIN¹

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During the course of certain clinical studies in the medical service of the Mayo Clinic with regard to the use of histamin in various types of hypertension, it was observed that, not infrequently, arrhythmia followed the hypodermic injection of 0.5 mg of histamin dichlorid. Since histamin dichlorid was found by Barger and Dale² and by Ackermann and Kutscher³ to be one of the ergot bases which are capable of causing intense tonic contraction of the uterus, attempts have been made to use it in the field of gynecology for the treatment of uterine inertia. Jager⁴ observed palpitation of the heart in the shocklike condition induced by a hypodermic administration of from 6 to 8 mg of histamin hydrochlorid to adults. Schenk⁵ noted that following the subcutaneous administration of histamin phosphate, in doses of from 4 to 5 mg, the pulse rate was doubled, with a marked fall in the blood pressure. However, there are no clinical observations on record of arrhythmia due to administration of histamin.

Dale and Laidlaw⁶ found, in experiments on cats kept under artificial respiration after the chest had been opened, that immediately following the intravenous injection of a large dose of histamin transient distention of the right side of the heart occurred with weakened and irregular contractions of the right ventricle, and that in an extreme case there was ventricular fibrillation, leading to the death of the animal. They considered the distention of the right side of the heart due to the constriction of the pulmonary arteries. In an experiment on

* This work was done under the supervision of Dr F A Willius

1 Barger, G., and Dale, H H. The Presence in Ergot and Physiological Activity of B-Imidazolylethylamine, *J Physiol* **40** xxxviii-xl, 1910, Chemical Structure and Sympathomimetic Action of Amines, *J Physiol* **42** 19-59, 1910

2 Ackermann, D., and Kutscher, F. Untersuchungen über die physiologische Wirkung einer Secalebase und des Imidazolylathylamins, *Ztschr f Biol* **54** 387-394, 1910

3 Jager, F. Ein neuer, für die Praxis brauchbarer Sekaleersatz (Tenosin), *Munchen med Wchnschr* **2** 1714-1715, 1913

4 Schenk, P. Ueber die Wirkungsweise des B-Imidazolylathylamins (Histamin) auf den menschlichen Organismus, *Arch f exper Path u Pharmakol* **89** 332-339, 1921

5 Dale, H H., and Laidlaw, P P. Histamin Shock, *J Physiol* **52** 355-390 (March) 1919

the heart-lung preparation from a dog, Fühner and Starling⁶ observed that on adding histamin to the circulating blood, the heart soon failed and dilated, and the pressure rose in the left auricle Einis⁷ found, in the isolated frog's heart, that small doses of histamin induced slowed and slightly intensified contraction of the heart, while large doses caused periodic cessation of the contraction, which produced a type of contraction of the heart comparable with "group contraction" of Luciani. On the isolated heart of the rabbit, perfused with Ringer's solution by the

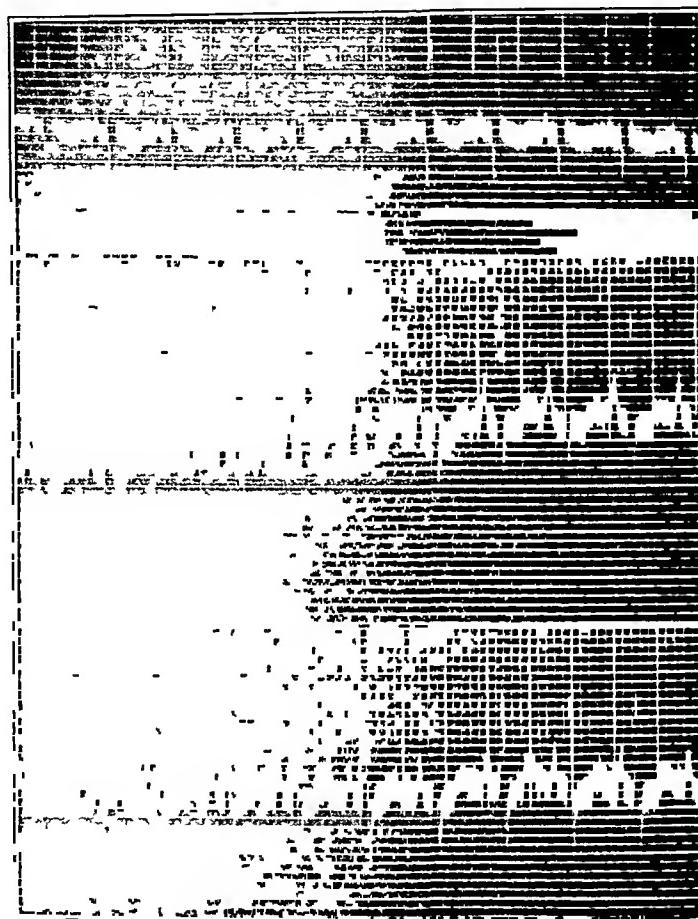


Fig 1 (Experiment 1)—Electrocardiograms taken with intact vagi, under ether anesthesia, before histamin injection Derivation I, P-R interval, 0.08 second, heart rate, 205 each minute, T wave inverted Derivation II, P-R interval, 0.08 second, heart rate, 200 each minute Derivation III, P-R interval, 0.08 second, heart rate, 187 each minute

use of Langendorff's apparatus, Einis observed that 0.5 c.c. of 0.1 per cent solution of histamin caused quickening of the heart rate to nearly

⁶ Fühner, H., and Starling, E. H. Experiments on the Pulmonary Circulation, *J. Physiol.* **47** 286-304, 1913-1914

⁷ Einis, W. Ueber die Wirkung des Pituitrins und B-Imidazoläthyamins (Histamins) auf die Herzaktion, *Biochem. Ztschr.* **52** 96-117, 1913

three times normal, with increased excursions of the heart action, which were later followed by slowing of the rate to less than the original. At the summit of this stimulating effect of the histamin, often extrasystoles supervened, each extrasystole being of about half the extent in excursion of immediately preceding systoles. In some of the similar experiments, he found, furthermore, that alternate auricular contractions were not followed by the ventricular contraction, and finally the ventricle ceased to respond to the auricular contractions, which were still progressing. He believed that this phenomenon was due to impaired auriculoventricular conduction. In another series of his experiments, made on rabbit's heart perfused with hirudinized blood, however, he failed to demonstrate

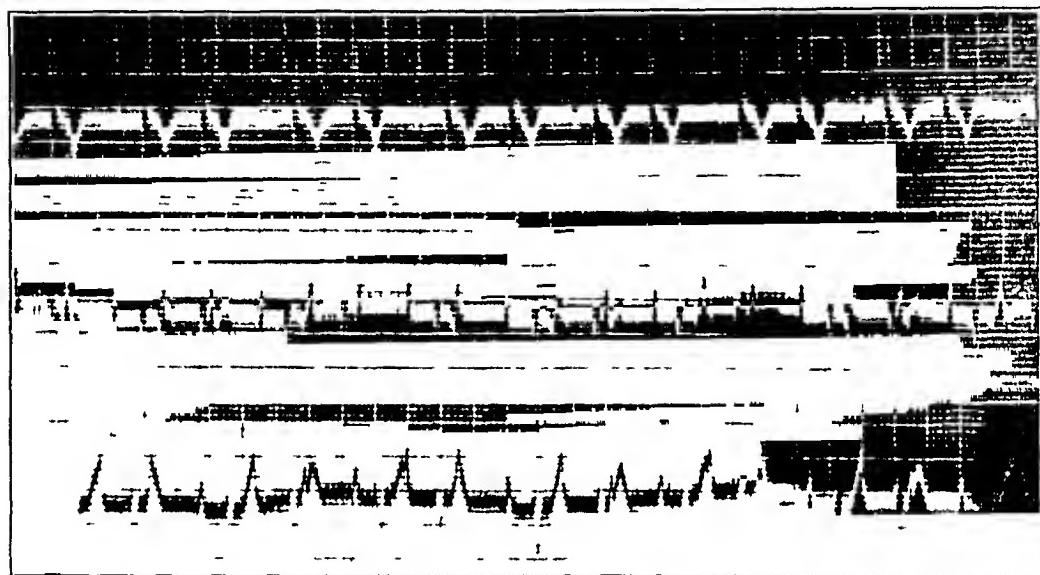


Fig. 2 (Experiment 1)—Electrocardiograms taken from one to six minutes following intravenous injection of 2 mg of histamin dichlorid for each kilogram of body weight. Complete auriculoventricular dissociation. Derivation I (from one to two minutes after injection of histamin), P-R interval variable, T wave inverted, auricular rate, 200 each minute, and ventricular rate, 133 each minute. Derivation II (from three to four minutes after injection of histamin), P-R interval variable, T wave inverted, auricular rate, 197 each minute, and ventricular rate, 125 each minute. Derivation III (five to six minutes after injection of histamin), P-R interval variable, Q-R-S complex notched, auricular rate, 193 each minute, and ventricular rate, 129 each minute.

the heart block, but saw only the quickening of the rate with increased excursion of the heart action which had been preceded by the slowing of slight degree and short duration. He regarded the quickening of the rate as an important part of the effect of histamin on the heart action, and thought that the slowing which follows the quickening in rabbit's heart perfused with Ringer's solution, might be due to exhaustion of the organ, as such slowing was missed in the preparation perfused with hirudinized blood.

In order to throw more light on the obscure points concerning the effect of histamin on the heart action, I have studied this effect carefully by means of electrocardiographic records

EXPERIMENTAL METHODS

Adult healthy dogs were employed for the experiments. To obtain electrocardiograms, the electrodes were applied to both forelegs and to the left hind leg. Some of the animals were anesthetized by ether, using the intratracheal insufflation method, others by a stomach tube, about one hour before the experiment, by the administration of from 1 to 1.5 gm of urethan for each kilogram of body weight. In some animals under ether anesthesia, both vagi, as they lay in the carotid sheath, were divided, about thirty minutes before the experiment. In some animals with intact or divided vagi, atropin sulphate was injected intravenously.

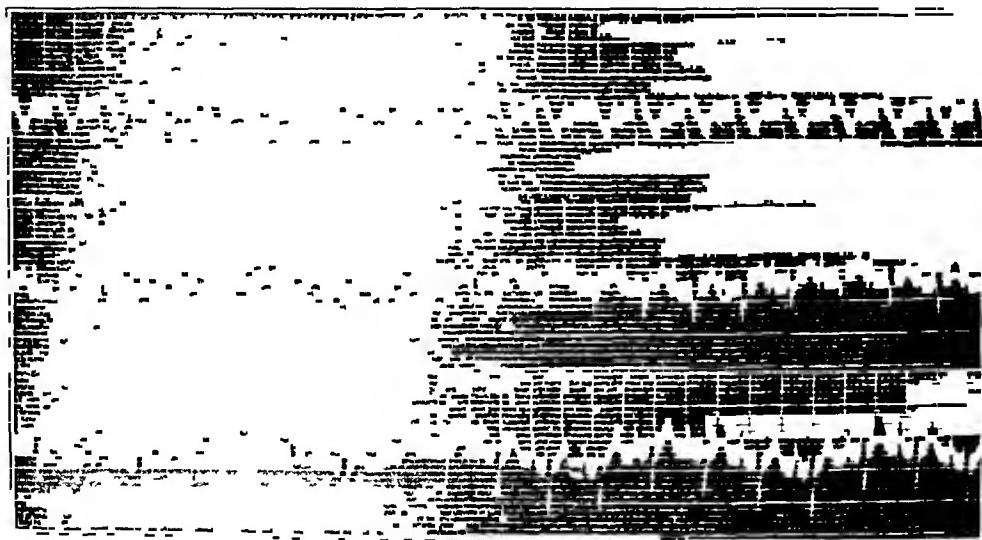


Fig. 3 (Experiment 1).—Electrocardiograms taken from eight to thirteen minutes after injection of histamin. Delayed auriculoventricular conduction and slowed heart rate. Derivation I (from eight to nine minutes after injection of histamin), P-R interval 0.16 second, T wave inverted, and auricular and ventricular rates the same, 191 each minute. Derivation II (from ten to eleven minutes after injection of histamin), P-R interval, 0.14 second, and auricular and ventricular rates the same, 191 each minute. Derivation III (from twelve to thirteen minutes after injection of histamin), P-R interval, 0.12 second, Q-R-S complex notched, auricular and ventricular rates the same, 180 each minute.

in doses of from 0.065 to 0.156 mg for each kilogram of body weight, for the purpose of paralyzing the vagi completely. The experiment on histamin was made at the period from four to twenty minutes after the injection of atropin.

A pure preparation of histamin dichlorid⁸ was used. Two milligrams of this drug for each kilogram of body weight were dissolved in small

⁸ This was obtained through the courtesy of Dr. Milton T. Hanke.

amounts of physiologic salt solution and were injected into the leg vein of a dog, and proved to be so toxic as to cause a chain of symptoms resembling those of anaphylactic shock, that is, stupor, fall in body temperature, cyanosis or flushing of the mucous membrane and the skin, slowed, and later quickened, weak and arrhythmic pulse, labored, slowed,

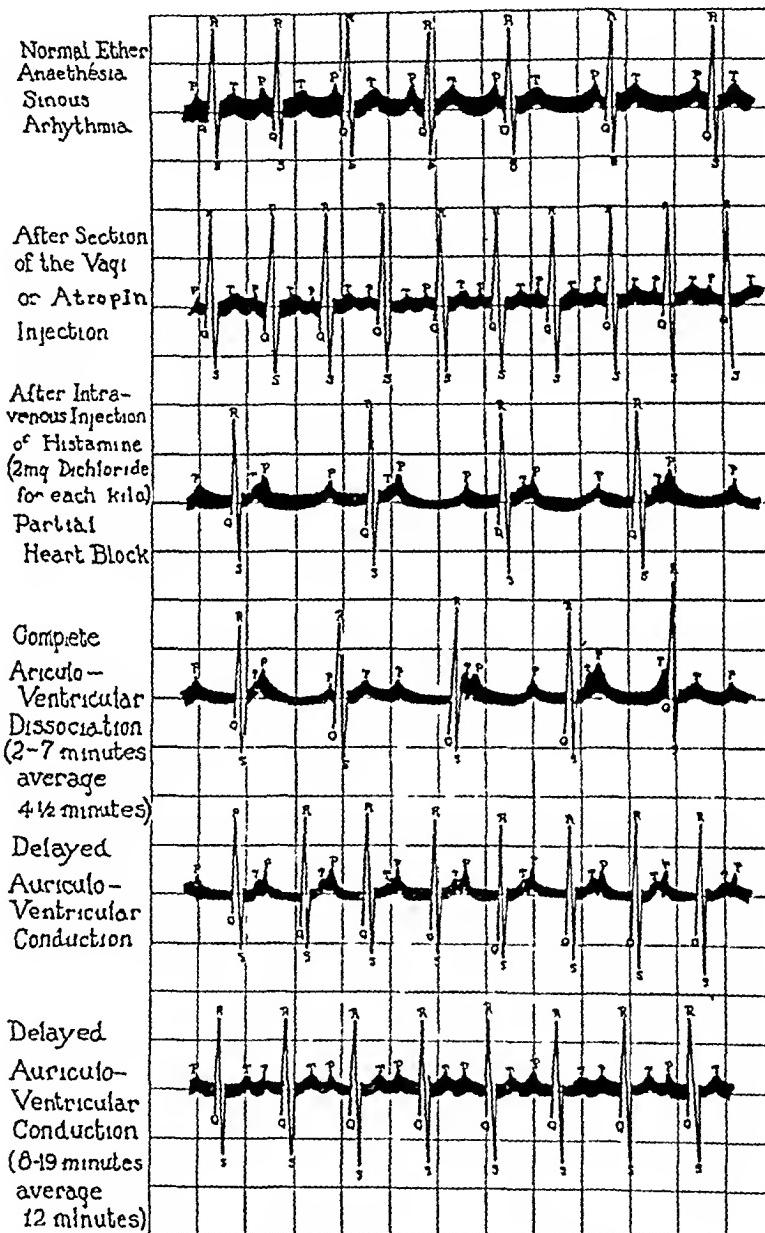


Fig 4.—Drawings of electrocardiograms

and later weakened respiration, defecation or tenesmus, and retching or vomiting. The mercury manometer, attached to a cannulated artery of the animal anesthetized by ether, showed a prompt fall of arterial blood pressure to a point lower than 40 mm, immediately following the injection of histamin. The fall persisted for a period of from a half-hour to two hours. If not anesthetized with ether or urethan, the dogs

recovered nearly completely from the shocklike condition within from ten to thirty minutes. Slight anesthesia with ether or urethan, under which the animals were kept during the procedure of taking the electrocardiograms, more or less intensified the intoxication, but most of the animals recovered within one or two hours.

EXPERIMENTAL OBSERVATIONS

EXPERIMENT 1—Dog 1, a male, adult mongrel, weighing 6.34 kg., with intact vagi, received 13 mg of histamin dichlorid, dissolved in 10 cc of physiologic sodium chlorid solution, injected intravenously. The animal remained under ether anesthesia while the electrocardiograms were taken (Table 1).

Complete auriculoventricular dissociation occurred from one to six minutes after the injection. In the electrocardiogram taken at this period, the auricular rate was almost unchanged, the P waves occurred at regular intervals, but they bore no regular relationship to the Q-R-S complexes. The ventricular rate was markedly slowed to less than two-thirds of the auricular and was arrhythmic. Exaggerated S waves in Lead III indicated the preponderance of the left ventricle. At the period of from eight to thirteen minutes after the injection of histamin, the P-R intervals became constant, but evidently much prolonged. The Q-R-S complexes were notched and still directed downward in Lead III. The electrocardiograms taken later than twenty-eight minutes after the injection showed nothing abnormal except a slightly slowed heart rate (Figs. 1, 2 and 3).

EXPERIMENT 2—Dog 2, a female mongrel, weighing 6.18 kg., with both vagi divided, under ether anesthesia, thirty minutes before the taking of the electrocardiogram, during which little ether was added, was injected intravenously with 12 mg of histamin dichlorid in 10 cc of physiologic sodium chlorid solution.

In the electrocardiogram (Table 2) taken from one to four minutes after the injection, the auricular rate was slowed, but was not arrhythmic. The P-R intervals were strikingly prolonged, and here and there the P wave was not followed by the ventricular complex which should respond to it, that is, delayed auriculoventricular conduction with partial heart block. The P wave in Lead II was notched, but not changed in its amplitude. At the end of the period of eight minutes after the injection, the conduction time returned to the original length.

EXPERIMENT 3—Dog 3, a male mongrel, weighing 6 kg., was given 6 gm of urethan by stomach tube, one hour before the experiment. Both vagi were cut under slight ether anesthesia. Twelve milligrams of histamin dichlorid in 8 cc of physiologic sodium chlorid solution was injected intravenously.

In the electrocardiogram (Table 3) taken from one to two minutes after the injection, there were evidences indicative of partial heart block. The P waves occurred at regular, but prolonged intervals. The Q-R-S complexes following every second P wave, however, were absent in the first portion of the tracing, in its middle portion following every third P wave, and in the latter portion following every fourth to sixth P wave. In the electrocardiogram taken later than six minutes after the injection, there was slight prolongation of the P-R intervals which returned to normal within about ten minutes after the injection, and slightly slowed heart rate, but no auriculoventricular dissociation was noticeable after this.

EXPERIMENT 4—Dog 4, a male, adult poodle, weighing 10.85 kg., had both vagi divided, under ether anesthesia, thirty minutes before the experiment. The animal, having been well trained, needed no anesthesia for the taking of electrocardiograms. Fourteen milligrams of histamin dichlorid, dissolved in 6 cc of physiologic sodium chlorid solution, was injected intravenously.

TABLE I—Results in Experiment 1

Electrocardiogram

		Intervals, Second						Amplitude, Millivolt						Rate		Remarks	
	Number	Lead	P-R	Q-R-S	S-T	P	Q	R	S	T	A	V					
April 29, 1924																	
Before injection of histamin	1	I	0.05	0.03	0.13	3	5	11	0	-2	205	205					
	1	II	0.08	0.03	0.17	5	2	14	5	-4	200	200					
	1	III	0.05	0.04	0.16	4.5	0	12	6	4	187	187					
After injection of histamin																	
From 1 to 2 minutes	2	I	0.16-0.24	0.04	0.14	3	6	12	0	-3	200	133	Complete auriculoventricular dissociation. Left ventricular preponderance. Respiration slowed and labored.				
3 to 4 minutes	2	II	0.20-0.26	0.04	0.14	5	3.5	9	5	-3.5	197	125					
5 to 6 minutes	2	III	0.16-0.28	0.05	0.16	5	0	5	9	6	193	129					
8 to 9 minutes	3	I	0.16	0.04	0.18	3	6	15	0	-4.5	191	191	Delayed auriculoventricular conduction. Notched Q-R-S in Lead III. Left ventricular preponderance.				
10 to 11 minutes	3	II	0.14	0.04	0.16	5	6.5	11	0	-4	191	191					
12 to 13 minutes	3	III	0.12	0.03	0.14	5	0	3	8	4.5	180	180					
15 to 19 minutes	4	II	0.09	0.04	0.12	1	1	5	5	-3	175	175					
28 minutes	5	II	0.08	0.04	0.12	1	1	8	4	-3	180	180					
	5	III	0.08	0.04	0.12	4.5	4	7.5	4	-3.5	171	171					
	5	II	0.08	0.04	0.12	4.5	4	7.5	4	-3.5	176	176					

TABLE 2—Results in Experiment 2

Electrocardiogram

		Intervals, Second						Amplitude, Millivolt						Rate		Remarks		
	Number	Lead	P-R	Q-R-S	S-T	P	Q	R	S	T	A	V						
May 6, 1924																		
Before injection of histamin	1	I	0.11	0.05	0.17	1	1	12	2	-3	144	144	Notched Q-R-S, left ventricular preponderance					
	1	II	0.11	0.05	0.16	6.5	1	15	5	-3	150	150						
After injection of histamin		III	0.09	0.04	0.19	5	1	15	11	3	150	150						
From 1 to 4 minutes	2	I	0.32	0.06	0.18	5	7	11	2	-4	135	109	Delayed auriculoventricular conduction. Periods of partial heart block, 2.1 Notched P in Lead II, slurred or notched Q-R-S in all leads, left ventricular preponderance, labored respiration, salivation.					
	2	II	0.26	0.05	?	3	6.5	9.5	4	-3	131	131						
	2	III	0.26	0.05	?	3	2	7	7	Trace	132	132						
5 to 8 minutes	3	I	0.13	0.05	0.16	4.5	7	12	0	-4	133	133						
	3	II	0.12	0.05	0.17	5	6	13	2	4	131	131						
	3	III	0.11	0.04	?	3	8	4	4	2	Trace	138	138					
10 to 13 minutes	4	I	0.12	0.05	0.16	4	5	10	4	-3	136	136						
	4	II	0.13	0.05	0.17	3.5	1	10	4	2	120	120						
	4	III	0.10	0.04	?	1	0	5	9	0	129	129						
15 to 18 minutes	5	I	0.10	0.04	0.16	4	6	12	0	-3	133	133						
	5	II	0.12	0.04	0.16	5	4	10	4	1	133	133						
	5	III	0.11	0.04	0.19	3	1	7	2	1	127	127						

In the electrocardiograms (Table 4), taken from fifteen seconds to one minute following the injection, the ventricular complexes that should have immediately followed every second P wave were absent. The auricular rate was slightly slowed and regular. The P-R intervals were prolonged though constant, that is, the partial heart block was in the rate of 2:1. At the period of from one and one-fourth to five and one-fourth minutes, the electrocardiograms showed that the P waves, although they occurred at regular intervals, bore no relationship to the ventricular complexes. The ventricular rate was slowed to about one-half of the auricular rate, and was more or less arrhythmic. In the electrocardiograms taken from seven and one-half to eight and three-fourths minutes after the injection, the P-R intervals were slightly prolonged, and the rate of both auricular and ventricular contractions was more or less slowed, but no dissociation between them was apparent. More than eleven minutes after the injection, there was nothing abnormal, except a slightly slowed heart rate.

EXPERIMENT 5—Dog 5, a male, adult mongrel, weighing 5 kg, had both vagi divided, under procain anesthesia, a half-hour before the experiment. No anesthesia was induced during the taking of the electrocardiograms. Ten milligrams of histamin dichlorid, dissolved in 5 cc of physiologic sodium chlorid solution, was injected intravenously.

The occurrence of complete auriculoventricular dissociation was indicated by electrocardiography (Table 5) from one-fourth to five and one-half minutes following the injection. Although the P waves occurred at regular intervals and in the rate nearly similar to that before the injection, they did not keep constant relation to the ventricular complexes. Within one minute after the injection, the ventricular rate was slowed to about one-half the auricular rate, but later it was gradually quickened, so that toward the end of five minutes it nearly equaled the auricular rate. The ventricular contractions were more or less arrhythmic, while the auricular were very regular. The tracing taken later, at from nine to ten minutes after the injection, showed slightly prolonged P-R intervals, but no further abnormal changes.

EXPERIMENT 6—Dog 6, a male, adult mongrel, weighing 5.56 kg, had both vagi cut, under ether anesthesia, thirty minutes before the experiment. No more ether was given during the taking of the electrocardiograms. Eleven milligrams of histamin dichlorid, dissolved in 6 cc of physiologic sodium chlorid solution, was injected into the leg vein.

In the electrocardiograms (Table 6) taken from one-half to one and three-fourths minutes after the injection, the P waves, although occurring at regular intervals, bore no relationship to the Q-R-S complexes, the P-R intervals showing great variation. Although the auricular rate was not much changed, compared with that before the injection, the ventricular rate was slowed to the extent of nearly two thirds of the auricular rate, and was slightly arrhythmic. In the tracing taken from one and three-fourths to four minutes after the injection there was slight prolongation of the P-R intervals and slight slowing of both the auricular and ventricular rates, but no auriculoventricular dissociation was indicated.

EXPERIMENT 7—Dog 7, a female, adult mongrel, weighing 8 kg, was electrocardiographed with the vagus intact.

The animal was kept under ether anesthesia during the taking of the electrocardiograms (Table 7). For the purpose of paralyzing the vagus, 0.5 mg of atropin sulphate, dissolved in 4 cc of physiologic sodium chlorid solution, was injected intravenously. Four minutes later, when the effect of atropin had evidently been indicated on the electrocardiograph, 16 mg of histamin dichlorid, dissolved in 4 cc of physiologic sodium chlorid solution, was injected intravenously. Before the injection of atropin, the dog showed sinus arrhythmia. All complexes in the tracings were found to maintain their proper relationship to one another, but there was a cyclic variation of the heart rate from 200 to 240, or from 143 to 214.

TABLE 3—Results in Experiment 3

Electrocardiogram

	July 14, 1924	Number	Lead	Intervals, Second			Amplitude, Millivolt				Rate V	Remarks
				P-R	Q-R-S	S-T	P	Q	R	S		
Before injection of histamin	1	I	0.08	0.01	0.11	1.5	3	3	1	-1	250	Notched Q-R-S in Lead III
	1	II	0.08	0.01	0.11	1.5	2.5	0	2	2	250	Notched Q-R-S in Lead III
	1	III	0.08	0.03	0.11	3.5	0	2	2	2	250	Notched Q-R-S in Lead III
After injection of histamin												
From 1 to 133 minutes	2	I	0.16	0.01	0.11	2	1	5	0	-2	185	Partial heart block
	2	II	0.16	0.01	0.11	2	1	5	0	-2	180	Notched Q-R-S in Lead III
	2	III	0.12	0.01	0.13	1	2	6	0.5	-1.5	193	Notched Q-R-S in Lead III
2.5 to 6.5 minutes	2	I	0.11	0.01	0.13	1	0	2	1.5	-1.5	190	Notched Q-R-S in Lead III
6 to 6.5 minutes	3	I	0.11	0.01	0.12	2	1	2	0	-2	200	Notched Q-R-S in Lead III
7 to 7.5 minutes	3	I	0.10	0.01	0.16	1.5	4	1.5	1.5	-2	211	Left ventricular preponderance
8 to 8.5 minutes	3	I	0.09	0.05	0.13	3	0	1	3	-3	212	Left ventricular preponderance
11 to 11.5 minutes	4	I	0.08	0.01	0.11	2	1	1	1	-2	216	Left ventricular preponderance
12 to 12.5 minutes	4	I	0.08	0.01	0.13	1	3	1	1.5	-2	225	Notched Q-R-S in Lead III
13 to 13.5 minutes	4	I	0.08	0.01	0.12	3	0	1	3	-3	225	Notched Q-R-S in Lead III
16.5 to 16.75 minutes	5	I	0.18	0.01	0.11	2	1	5	0	-2	220	Notched Q-R-S in Lead III
17 to 17.25 minutes	5	I	0.08	0.01	0.12	3	0	1	2.5	-2.5	220	Notched Q-R-S in Lead III
17.5 to 17.75 minutes	5	I	0.08	0.04	0.12	3	0	1	3	-3	220	Notched Q-R-S in Lead III

TABLE 4—Results in Experiment 4

Electrocardiogram

	July 21, 1924	Number	Lead	Intervals, Second			Amplitude, Millivolt				Rate V	Remarks
				P-R	Q-R-S	S-T	P	Q	R	S		
Before injection of histamin	1	I	0.06	0.03	0.09	1.0	2.0	3.0	0.0	-1.0	262	Partial heart block, 2 1
	1	II	0.06	0.03	0.09	2.0	1.0	6.0	1.0	-1.5	262	Respiration labored and frequent
	1	III	0.07	0.03	0.10	2.5	1.0	6.5	1.0	-1.0	262	Defecation
After injection of histamin												
From 0 to 50 minutes	2	I	0.18	0.03	0.18	1.0	2.0	3.5	1.0	-1.0	220	Salivation
0.75 to 1.0 minutes	2	II	0.18	0.03	0.20	2.5	0.0	6.0	1.0	-3.5	220	Complete A-V dissociation
1.25 to 1.50 minutes	2	III	0.18-0.17	0.03	0.16	1.5	0.0	6.5	1.0	-2.5	211	Defecation
	2	II	0.13-0.20	0.03	0.13	2.0	0.0	6.0	1.0	-2.0	207	Salivation
	2	II	0.13-0.24	0.03	0.14	2.0	0.0	6.0	1.0	-2.0	212	Notched P and Q-R-S
	2	II	0.12-0.24	0.03	0.14	2.0	0.0	6.0	1.0	-2.0	182	Exaggerated P
	2	II	0.12-0.26	0.03	0.15	2.5	0.0	6.5	1.0	-3.0	216	Notched P and Q-R-S
	2	II	0.03-0.10	0.04	0.15	2.5	0.0	6.5	1.0	-1.0	214	Exaggerated P
1.75 to 2.25 minutes	2	I	0.14	0.02	0.10	0.5	1.0	2.0	0.5	-1.5	210	Exaggerated P
	2	II	0.12	0.03	0.12	1.5	0.5	3.0	1.0	-1.5	212	Exaggerated P
	2	III	0.12	0.03	0.12	1.0	0.5	3.0	1.0	-1.5	212	Exaggerated P
7.50 to 7.75 minutes	3	I	0.14	0.02	0.10	0.5	1.0	2.0	0.5	-1.5	210	Exaggerated P
8.0 to 8.25 minutes	3	II	0.12	0.03	0.12	1.0	0.5	3.0	1.0	-1.5	212	Exaggerated P
8.50 to 8.75 minutes	3	II	0.12	0.03	0.12	1.0	0.5	3.0	1.0	-1.5	212	Exaggerated P
11.0 to 11.25 minutes	4	I	0.08	0.02	0.12	1.5	2.0	5.0	0.5	-2.0	220	Exaggerated P
11.5 to 11.75 minutes	4	I	0.08	0.03	0.15	3.5	1.5	5.0	0.0	-4.0	225	Exaggerated P
12.0 to 12.25 minutes	4	I	0.08	0.03	0.12	1.5	2.0	6.0	0.0	-5.0	225	Exaggerated P
16.0 to 16.25 minutes	5	II	0.06	0.03	0.11	2.0	0.0	3.0	1.0	-3.5	229	Exaggerated P
16.5 to 16.75 minutes	5	II	0.06	0.03	0.12	3.0	0.0	3.0	1.0	-2.5	225	Exaggerated P
17.0 to 17.25 minutes	5	III	0.06	0.03	0.12	3.0	0.0	3.0	1.0	-2.5	225	Exaggerated P

After the injection of atropin, sinus arrhythmia disappeared completely. The P-R intervals were slightly shortened, and the heart rate was accelerated. Immediately following the injection of histamin, the P-R intervals were markedly prolonged, and every second P wave was not succeeded by the ventricular complex. The ventricular rate was reduced to about one-half the auricular rate. This period of partial heart block was followed by a period of complete auriculoventricular dissociation. The P waves lost their proper relationship to the Q-R-S complexes, and the P-R intervals were variable. The ventricular rate, which had been much slowed, showed a tendency to approach the auricular rate. At the end of the period of eight minutes after the injection of histamin, there was no indication of the auriculoventricular dissociation, but the P-R intervals were still prolonged. As the accelerated rate had continued, the P waves were superimposed on, or buried in, the preceding ventricular complex. A part of the tracing, therefore, resembled that of nodal rhythm. Thirteen minutes after the injection, nothing abnormal was found in the tracing, except slightly prolonged P-R intervals and diminished amplitude of Q-R-S complexes. Absence of the sinus arrhythmia and presence of the accelerated rate suggested that there was still paralysis of the vagus induced by the atropin.

EXPERIMENT 8—Dog 8, a female, adult mongrel, weighing 128 kg, had both vagi divided, under ether anesthesia, forty minutes before the experiment. For the purpose of paralyzing the vagi completely, 1 mg of atropin sulphate, dissolved in 4 cc of physiologic sodium chlorid solution, was injected twice intravenously, with an interval of ten minutes. Twenty-one milligrams of histamin dichlorid, dissolved in 4 cc of physiologic sodium chlorid solution, was injected intravenously five minutes after the second injection of atropin.

During the taking of the electrocardiograms (Table 8), the animal was kept under ether anesthesia. There were no notable changes in the electrocardiogram after the injection of atropin. A continuous electrocardiographic tracing in the second derivation was taken, from one to ten minutes following the injection of histamin. From one to four minutes after, complete auriculoventricular dissociation occurred. The P waves occurred at regular intervals, but bore no relationship to the ventricular complexes, the P-R intervals being variable. The P waves often were superimposed on the R or T waves. Synchronous occurrence of the P waves with the R or the T waves was indicated by a conspicuously greater amplitude of the latter. The auricular rate was slightly slowed. The ventricular contractions were arrhythmic and of lower rate than the auricular. Toward the end of four minutes, the ventricular rate was approaching the auricular.

From five to seven minutes after the injection of histamin, both the auricular and the ventricular contractions occurred at the regular and the similar intervals. In the first part of this period, the P and the T waves occurred synchronously, producing single waves of comparatively high amplitude. In the last part of the period there was still the confluence of the P and the T waves although their peaks were distinguishable from each other. From eight to ten minutes after the injection of histamin, nothing abnormal was noted, except a more or less lengthened conduction time.

EXPERIMENT 9—Dog 9, a female, adult mongrel, weighing 107 kg, had both vagi divided, under ether anesthesia, thirty minutes before the experiment. During the taking of the electrocardiograms (Table 9), the animal was kept under ether anesthesia. One milligram of atropin sulphate, dissolved in 4 cc of physiologic sodium chlorid solution, was injected intravenously. Nine minutes later, 22 mg of histamin dichlorid, dissolved in 2 cc of physiologic sodium chlorid solution, was injected intravenously. A continuous electrocardiographic record in the second derivation was taken from one-fourth to five and one-half minutes after the injection of histamin. Six minutes after the injection of atropin, there was a gradual decrease in amplitude of the P waves, as well as of the Q-R-S complexes. The R waves were slurred.

TABLE 5—Results in Experiment 5

Electrocardiogram										Rate			Remarks	
			Intervals, Second			Amplitude, Millivolt								
	Number	Lead	P-R	Q-R-S	S-T	P	Q	R	S	T	A	V		
July 22, 1924														
Before injection of histamin	1	I	0.08	0.06	0.12	2	0	9	0.5	2	229	229	Slurred or noted Q-R-S in Leads I and II; exaggerated P in Leads II and III	
	1	II	0.08	0.04	0.13	5	0	8	2	3	228	228		
	1	III	0.08	0.04	0.14	5	1	6	3	2	228	228		
After injection of histamin														
From 0.25 to 0.5 minutes	2	I	0.18	0.05	0.14	2	0	10	0.5	6	229	115	Partial heart block, 2:1	
0.75 to 1 minute	2	II	0.18	0.05	0.20	5	4	7.5	1	8	229	115	Complete auriculoventricular dissociation	
1.5 to 1.75 minutes	2	III	?	0.04	0.18	2	8	4	1	5	233	150		
2 to 5.5 minutes	2	I	?	0.04	0.16	4	2	2	8	0	225	172	Restless a few seconds immediately following the injection, but later calm	
	2	II	?	0.04	0.16	3	2	8	0	1	229	176	Respiration slowed, salivation	
	2	III	0.20-0.24	0.04	0.12	4	3	8	0	1	225	200	Notched Q-R-S in Lead II	
9 to 9.25 minutes	2	I	0.20	0.04	?	4	3	7	1	?	232	230	Left ventricular preponderance	
9.5 to 9.75 minutes	3	I	0.11	0.04	0.12	2	2	10	0	1	225	225		
10 to 10.25 minutes	3	II	0.12	0.04	0.10	3	3	3	0	2	229	229		
10 to 10.25 minutes	3	III	0.10	0.04	0.16	4	3	10	3	3	218	218		
14 to 14.25 minutes	4	I	0.08	0.03	0.08	0.16	2	1	4	1	214	214	Left ventricular preponderance	
16.25 to 16.5 minutes	4	II	0.08	0.03	0.08	0.16	4	6	0	3	210	210		
18 to 18.25 minutes	4	III	0.08	0.03	0.10	1	4	7	1	3	214	214	Notched Q-R-S in Lead I	
19 to 19.25 minutes	5	I	0.08	0.04	0.16	2	1	8	0	3	218	218	Left ventricular preponderance	
19.5 to 19.75 minutes	5	II	0.08	0.03	0.16	3	2	6	0	2	225	225		
20 to 20.25 minutes	5	III	0.08	0.03	0.16	4	3	6	0	0	225	225		
24 to 24.25 minutes	6	I	0.08	0.04	0.15	2	0	7	0	1	225	225	Notched Q-R-S in Leads I and II	
24.5 to 24.75 minutes	6	II	0.08	0.04	0.16	2	1	9	0	2	225	225	Left ventricular preponderance	
25 to 25 minutes	6	III	0.08	0.04	0.16	4	6	9	1	2	225	225		

TABLE 6.—Results in Experiment 6

July 23, 1924										Electrocardiogram				Remarks	
Before injection of histamin					Intervals Second					Amplitude Millivolt				Rate	
Number	Lend	PR	Q R S	S-T	P	Q	R	S	T	A	V				
1	I	0.06	0.04	0.12	1	0	6	0	-0.5	220	220	Fraggerated P in Lend II and III			
	II	0.06	0.04	0.16	4	0	11	0	-1	220	220				
	III	0.06	0.04	0.12	1	1	9	1	-1.5	220	220				
1	I	0.10	0.16	0.03	0.16	2	1	6	2	220	133	Complete turrenloventricular dissociation, slurred Q R-S in Lead III			
	II	0.10	0.16	0.04	0.16	4	1	10	1.5	218	170				
	III	0.10	0.16	0.04	0.16	1	1	10	2	218	171				
From 0.5 to 1.75 minutes	2	I	0.12	0.18	0.03	0.12	3	0	5	210	171				
1 to 1.25 minutes	2	II	0.12	0.03	0.14	2.5	1	7	1	210	195				
	III	0.10	0.02	0.14	2	0.5	2	5	1	180	180				
1.75 to 4 minutes	2	I	0.10	0.02	0.14	2	0.5	7	5	180	180				
	II	0.08	0.03	0.15	2	0.5	7	1	1	180	180				
	III	0.08	0.03	0.12	1	1	5	5	3	180	180				
6.5 to 6.75 minutes	2	I	0.08	0.03	0.12	1	1	5	3	240	240				
7 to 7.25 minutes	3	II	0.07	0.04	0.14	5	0	11	3	240	240				
7.25 to 7.5 minutes	3	III	0.07	0.03	0.12	3.5	0	8	2	250	250				
10.5 to 10.75 minutes	4	I	0.07	0.03	0.12	1.5	0	3	2	250	250				
11 to 11.25 minutes	4	II	0.07	0.03	0.12	3.5	0	7.5	0	222	222				
12.5 to 12.75 minutes	4	III	0.06	0.03	0.12	4	0	0	0	218	218				

TABLE 7.—Results in Experiment 7

Sept 10, 1924	Time	Injection	Number	Lead	Electrocardiogram												Remarks	
					Interval			Second			Amplitude, Millivolt			Rate				
					P	R	S	Q	R	S	P	Q	R	S	T	V		
0 30 a m			1	II	0.06	0.03	0.12	5	3	18	17	4	200-240	200-240	213-214	Partial heart block, 2:1		
0 33 1 m	Atropin, 0.5 mg intravenously	1	II	0.06	0.03	0.12	15	4	20	18	4	143-214	143-214	143-214	Complete auriculoventricular dissociation			
0 35 1 m		2	II	0.05	0.03	0.12	15	3	14	15	4	271	271	271	Delayed auriculoventricular conduction			
0 37 a m	Histamin, 16 mg intravenously															250		
After injection of hist min 0 37 1/2 a m																250		
0 25 minute			3	II	0.16	0.03	0.12	1	1	13	16	4	262	262	133			
			3	II	0.06-0.20	0.03	0.12	15	1	10	15	4	267	267	171			
			3	II	0.01-0.20	0.03	0.12	35	3	9	15	4	245	245	161			
			3	II	0.16	0.03	0.12	15	2	8	7	3	267	267	267			
			4	II	0.12	0.03	0.12	4	2	8	7	3	250	250	250			
			4	II	0.08	0.03	0.12	1	2	7	7	4	250	250	250			

TABLE 8—Results in Experiment 8

Sept 12, 1924			Injection	Num ber	Lead	Interval Second			Amplitude 10 ⁻⁴ Volt			Rate			Remarks	
Time				1	II	P-R	Q R S	S-T	P	Q	R	S	T	I	V	
11 52 a.m.			Atropin, 1 mg			0.07	0.03	0.12	?	3	18	4.5	4	207	207	
12 15 p.m.			Atropin, 1 mg													
12 25 p.m.																
12 26 p.m.																
12 30 p.m.			26 mg of hist- amin injected													
After injection of histamin																
12 31 p.m.			1 minute	3	II	?	0.03	0.12	?	3	17	5	6	191	150	
12 32 p.m.			2 minutes	3	II	?	0.03	0.12	6	3	18	6	7.8*	167	164	
12 33 p.m.			3 minutes	3	II	?	0.03	0.12	5	3	17	5	6.8*	167	164	
12 34 p.m.			4 minutes	3	II	?	0.03	0.12	1	3	14	17*	5	90	160	
12 35 p.m.			5 minutes	3	II	0.20	0.03	?	7*	3	14	5	8*	191	191	
12 36 p.m.			6 minutes	3	II	0.16	0.03	?	6*	3	14	5	7*	200	200	
12 37 p.m.			7 minutes	3	II	0.15	0.03	0.12	5.5*	3	14	5	6*	195	195	
12 38 p.m.			8 minutes	3	II	0.13	0.03	0.12	5.5	3	13	5	6	200	200	
12 39 p.m.			9 minutes	3	II	0.09	0.03	0.12	6	2.5	12	5	6	218	218	
12 40 p.m.																

* Figures denote amplitude of superimposed waves

TABLE 9—Results in Experiment 9

Sept 19, 1924			Injection	Num ber	Lead	Interval Second			Amplitude 10 ⁻⁴ Volt			Rate			Remarks	
Time				1	II	P-R	Q R S	S-T	P	Q	R	S	T	I	V	
10 01 1/2 a.m.			Atropin, 1 mg	1	II	0.08	0.04	?	6	3	16	7.5	?	218	218	
11 05 1/2 a.m.				2	II	0.08	0.04	?	5	3	12	7	?	200	200	
11 06 1/2 a.m.				2	II	0.08	0.03	?	3	2	?	?	?	200	200	
11 11 a.m.			22 mg of hist- amin injected	3	II	0.13	0.04	?	4.5	2.5	9	3	?	175	175	
11 14 a.m.				3	II	?	0.04	0.14	4	2	7	3	-1	171	142	
After injection of histamin																
11 14 1/2 a.m.			0.25 minutes	3	II	?	0.04	0.03	?	2	2	8	3	?	140	
11 15 a.m.			0.5 minutes	3	II	?	0.04	0.03	?	1	2.5	8	3	-3	138	
11 15 1/2 a.m.			1 minute	3	II	?	0.04	0.03	?	3	2.5	?	?	175	164	
11 16 a.m.			1.5 minutes	3	II	?	0.03	0.03	?	3	2.5	?	?	179	164	
11 16 1/2 a.m.			2 minutes	3	II	?	0.03	0.03	?	3	2.5	?	?	176	176	
11 16 1/2 a.m.			2.5 minutes	3	II	0.24	0.04	?	3	2	?	?	?	176	176	
11 17 1/2 a.m.			3 minutes	3	II	0.18	0.03	?	2.5	?	?	?	?	176	176	
11 17 1/2 a.m.			3.5 minutes	3	II	0.18	0.04	?	2.5	?	?	?	?	180	180	
11 18 1/2 a.m.			4 minutes	3	II	0.16	0.04	?	4	2.5	6	3	?	180	176	
11 18 1/2 a.m.			4.5 minutes	3	II	0.15	0.04	?	4	2.5	6	3	?	176	176	
11 19 a.m.			5 minutes	3	II	0.14	0.04	?	4	0	6	3	2	180	180	
11 19 1/2 a.m.			5.5 minutes	3	II	0.13	0.04	?	4	0	7	3.5	?	176	176	

* Figures denote amplitude of superimposed waves

The electrocardiogram, taken about fifteen seconds after the injection of histamin, showed prolonged P-R intervals and slightly increased amplitude of the P and R waves. Both the auricular and the ventricular rates were equally diminished, neither dissociation nor arrhythmia being shown. From one-half to two minutes after the injection of histamin, a complete auriculoventricular dissociation was indicated by the absence of regular relationship between the P waves and the Q-R-S complexes, the P-R intervals varying considerably. The ventricular complexes occurred at abnormal intervals, that is, every fourth or fifth interval, and during the latter stage of this period every sixth or seventh interval was irregularly prolonged, by from 30 to 50 per cent, as compared with the others which were nearly regular, although slightly longer than those of the auricular. From one to one and one-half minutes after the injection of histamin, instead of the P waves there occurred irregular waves, varying in rate, amplitude and contour, which appeared to reveal coarse, auricular fibrillation or impure flutter. More than two and one-half minutes after the injection of histamin, there was a considerable delay in the auriculoventricular conduction, but no dissociation. The heart rate was regular, though still slowed. The P waves were notched at the beginning of the period.

COMMENT

As has been shown in the foregoing electrocardiographic records, intravenous injection of histamin dichlorid, 2 mg for each kilogram of body weight, causes prompt changes in the auriculoventricular conduction. A delay in the conduction is clearly indicated by the lengthening of the P-R intervals. In twelve normal dogs with intact, as well as divided, vagi, kept under ether or urethan anesthesia, the P-R interval was found to range from 0.06 to 0.11 second, and to average 0.08 second. Within one minute after the injection of histamin, the conduction time, when it could be measured, was lengthened to more than 0.13 second, and in an extreme case, to 0.32 second. In the records taken as early as fifteen seconds after the injection of histamin, the prolongation of the conduction time was already evident. The return to the normal range of the conduction time occurred at the points of from two to thirteen minutes, an average of seven and one-half minutes after the injection. Complete return to the original conduction time was attained at from eight to nineteen minutes (an average of twelve and one-fourth minutes) after the injection. Complete auriculoventricular dissociation, partial heart block or both occurred in each instance following the injection. Three of nine dogs showed periods of both complete and partial heart block, four, complete auriculoventricular dissociation, and two others, only partial heart block. In four cases in which the electrocardiograms were taken as early as fifteen seconds after the injection of histamin, in three the period of partial heart block developed first, and it turned into that of complete auriculoventricular dissociation at from one to one and one-half minutes after the injection. In another case, complete auriculoventricular dissociation began one-half minute after the injection, without a preceding period of partial block. The complete or partial heart block disappeared at the end of the periods.

of from one and three-fourths to seven minutes (average four and one-half minutes) after the injection of histamin. Not infrequently, ventricular arrhythmia attended the auriculoventricular dissociation. Sometimes periodic occurrence of partial heart block produced irregular pulse. The impairment of the conduction, as described, seems not to be influenced by the administration of ether, urethan or procain for the purpose of anesthesia (Fig. 4).

Depression of the auriculoventricular conduction of the impulse may be induced by stimulation of the vagi, as has been shown by Mackenzie,⁹ and by Robinson and Draper.¹⁰ The depression of the conduction resulting from the administration of digitalis is partially or completely removed by atropin, as reported by Cohn and Fraser,¹¹ and by White and Sattler.¹² That histamin may stimulate the vagi has been suggested by a number of investigators. According to Barger and Dale, Dale and Lairdlaw, and Ackermann,¹³ histamin possesses a weak pilocarpin-like action on the glands, which can be completely abolished by atropin. Keeton, Koch and Luckhardt¹⁴ assert that the stimulating effect of histamin on the gastric secretion can be inhibited by atropin, but not completely, if the histamin is given in large doses. So far as I know, however, the disturbance in the auriculoventricular dissociation due to histamin cannot be prevented by the paralyzing of the vagi. In most of the animals in this series, the vagi were divided. To some of them, also, atropin was given in doses more than sufficient to paralyze the vagi completely. According to Pilcher and Sollmann,¹⁵ the dosage of atropin required to paralyze the vagi of dogs completely is between 0.01 and 0.075 mg for each kilogram of body weight, and its maximal effect lasts for from five to twenty minutes. In the present experiments, from 0.065 to 0.156 mg of atropin sulphate for each kilogram of body weight was injected intravenously, and the changes

⁹ Mackenzie, J. Definition of the Term "Heart-Block," *Brit M J* **2** 1107-1111, 1906.

¹⁰ Robinson, G C, and Draper, G. Studies with the Electrocardiograph on the Action of the Vagus Nerve on the Human Heart, II, The Effects of Vagus Stimulation on the Hearts of Children with Chronic Valvular Disease, *J Exper Med* **15** 14-48, 1912.

¹¹ Cohn, A E, and Fraser, F R. Certain Effects of Digitalis on the Heart, *J Pharmacol & Exper Therap* **5** 512, 1913-1914.

¹² White, P D, and Sattler, R R. The Effect of Digitalis on the Normal Human Electrocardiogram, with Especial Reference to A-V Conduction, *J Exper Med* **23** 613-630 (May) 1916.

¹³ Ackermann, D. Ueber den bakteriellen Abbau des Histidins, *Ztschr f physiol Chem* **65** 504-510, 1910.

¹⁴ Keeton, R W, Koch, F C, and Luckhart, A B. Gastrin Studies. Response of Stomach Mucosa to Food and Gastrin Bodies as Influenced by Atropin, *Am J Physiol* **51** 469 (April) 1920.

¹⁵ Pilcher, J D, and Sollmann, T. Quantitative Studies of Vagus Stimulation and Atropin, *J Pharmacol & Exper Therap* **5** 317-340, 1913-1914.

in the conduction due to histamin were produced at from four to nine minutes after atropin had been administered. It is evident, therefore, that the disturbances in the auriculoventricular conduction occurring after the injection of histamin are not due to stimulation of the vagus, neither its centers nor its endings.

As Roaf and Sherrington,¹⁶ Lewis, Mathison and Oppenheimer¹⁷ have shown, asphyxia causes profound disturbances in auriculoventricular conduction, the development of which is independent of the central nervous system. According to the results of electrocardiographic investigation by Lewis and his collaborators, the delay in the conduction and the heart block occur regularly within a few minutes of the cessation of respiratory ventilation in the intact curarized animal with or without vagal section, in the decerebrated and the spinal animal, and after atropinization. It is well known that histamin causes promptly severe respiratory difficulties, presumably by strong constriction of bronchioles and pulmonary vessels. Such embarrassment in the functioning of the lung and its circulation may result in acute asphyxia which is capable of inducing heart block, as has been shown. Greene and Gilbert,¹⁸ studying the blood pressure and electrocardiographic changes in dogs during extreme want of oxygen, showed that, in asphyxiation, there occurred inverted or suppressed P waves, partial or complete heart block, sometimes reversed rhythm, and ectopic beats. They noted, however, the complete disappearance of these changes after section of the vagi. Willius¹⁹ obtained electrocardiographic records from dogs, all of whose vessels leading to and from the heart were simultaneously and completely clamped, and demonstrated the occurrence of various types of nodal rhythm, sino-auricular block, delayed auriculoventricular conduction, and complete or partial heart block in this condition. He observed further, that after section of the vagi, an exactly similar procedure was not followed by the appearance of any of the foregoing changes. The disturbance of the heart's action induced by the injection of histamin in the present experiments is decidedly different from those observed by Greene and Willius in asphyxia in that the former still occurs after vagal section or atropinization.

16 Roaf, H. E., and Sherrington, C. S. Further Remarks on the Mammalian Spinal Preparation, *Quart J Exper Physiol* **3** 209-211, 1909-1910.

17 Lewis, T., and Mathison, G. C. Auriculoventricular Heart-Block as a Result of Asphyxia, *Heart* **2** 47-53, 1910-1911. Lewis, T., and Oppenheimer, B. S. The Influence of Certain Factors on Asphyxial Heart-Block, *Quart J Med* **4** 145-152, 1910-1911.

18 Greene, C. W., and Gilbert, N. C. Blood Pressure and Electrocardiographic Changes in the Dog During Extreme Oxygen Want, *Am J Physiol* **55** 307-308, 1921.

19 Willius, F. A. Changes in the Mechanism of the Human Heart Preceding and During Death, *M J & Record* **119** xlii-xlii (March 19) 1924.

There have been various clinical and anatomic observations suggesting that coronary sclerosis may be one of the important etiologic factors of the heart block, and that some ischemia of the auriculoventricular bundle may be responsible for the diminution and its conductivity. According to Dale²⁰ and his co-workers, histamin, if injected intravenously in a large dose, produces strong constriction of the arteries and oligemia due to retardation of blood flow in relaxed capillaries, and loss of plasma through abnormally permeable capillaries. It seems not unlikely that such vascular disturbance may interfere with the adequate blood supply of the tissues of the heart, and contribute to the development of impaired auriculoventricular conduction. Further investigations are desirable to establish the point whether or not histamin possesses a direct depressor action on the auriculoventricular bundle.

Taylor²¹ reported a case of transient heart block due to intestinal toxemia. A similar case was observed by Hirschfelder²² who asserted that ptomaine poisoning or auto intoxication due to severe gastro-intestinal disturbance may give rise to the heart block. Mellanby²³ suggested that some type of severe gastro-intestinal disturbance with diarrhea and vomiting in children may be due to absorption of histamin or the histamin-like substance formed in the intestinal tract. Gerard²⁴ suggested that histamin may be responsible for the toxemia in cases of intestinal obstruction. The present investigation adds further evidence that histamin can cause striking disturbances in the auriculoventricular conduction.

SUMMARY

Histamin, if injected intravenously into dogs in a dose of 2 mg of its dichlorid for each kilogram of body weight, promptly caused a delay in the auriculoventricular conduction, and transient, complete or partial heart block. The average duration of the delayed conduction was approximately twelve minutes following the injection of histamin, and that of heart block four and one-half minutes. The foregoing disturbances in conduction occur even after vagal section or atropinization.

20 Dale, H. H., and Richards, A. N. The Vasodilator Action of Histamin and of Some Other Substances, *J. Physiol.* **52** 110-165 (July) 1918. Dale and Laird (Footnote 5).

21 Taylor, F. L. A Case of Transient Heart Block Due to Intestinal Toxemia, *J. A. M. A.* **50** 1246-1247 (April 18) 1908.

22 Hirschfelder, A. D. Diseases of the Heart and Aorta, Ed. 3, Philadelphia, J. B. Lippincott Company, 1918, p. 581.

23 Mellanby, E. An Experimental Investigation on Diarrhea and Vomiting of Children, *Quart. J. Med.* **9** 165-215, 1915-1916.

24 Gerard, R. W. Chemical Studies on Intestinal Intoxication, I, The Presence and Significance of Histamin in an Obstructed Bowel, *J. Biol. Chem.* **52** 111-124 (May) 1922.

MEASUREMENT OF THE BODY SURFACE IN MEN AND IN WOMEN

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Practical determination of the body surface is a question of the highest importance, as indicated by the numerous contributions on the subject. The present discussion deals with a practical method for making such determinations. First, however, it is well to review the work of the physiologists, which is employed by physicians as a basis.

Recent clinical studies of the basal metabolism have confirmed the importance of the law that surface is an important factor in animal thermogenesis¹. This law, perceived by Bergman,² in 1848, was first fully formulated by Rubner,³ in 1883, following his combustion tests, and by Richet,⁴ whose studies of 1884 and 1885 refer to calorimetric measurements. It shows that animal thermogenesis is fundamentally expressed in terms of the cutaneous surface, and not on the volume or weight. Figures obtained by various observers appear in the accompanying table.

Comparative Body Measurements of Different Observers

Observers	Body Weight, Kg	Gross Calories of the Ration	Calories per Square Meter
Rubner	67	3,094	1,520
Voit and Pettenkofer	70	3,054	1,470
Lapicque and Marette	73	3,027	1,420
Hirschfeld	73	3,818	1,560
Tsobci and Murito	46	2,855	1,430
Kumagaya	48	2,478	1,550

This table shows the practical constancy of heat expenditure per square meter, regardless of variations in body weight. Voit's statement that heat expenditure for animals analogous with respect to this single factor is uniformly equivalent to 1,000 calories per square meter has been clearly proved inexact by M and L Lapicque⁵. The latter have

* These results were first reported, Feb 25, 1924.

* Translated by Theodore C Merrill, Paris, 10 bis rue Herran.

1 Benedict, F G, and Talbot, F B Metabolism of Growth from Birth to Puberty, Carnegie Institute Publication, No 302, 1921.

2 Bergman Wärmeökonomie der Thiere, Gottingen, 1848.

3 Rubner, M Ueber den einfluss der Körpergrösse auf Stoff und Kraftwechsel, Ztschr f Biol 19 545, 1883.

4 Richet, C Mesure des combustions respiratoires chez le chien, Arch f Physiol 2 17-30 (Jan) 1890, Mesures de calorimetrie, Arch f Physiol 6 237, 450-497 (Aug -Sept) 1885.

5 Lapicque, M, and Lapicque, L Compt rend Soc de Biol 66 289 (Feb 20) 1909, ibid 66 528 (March 27) 1909, ibid 67 337 (July 31) 1909, ibid 70 375 (March 11) 1911, ibid 70 737 (May 13) 1911, Bull Soc d'hyg aliment, Nos 5 and 6, 1911, Bull du Museum d'hist nat, No 1, 1911, p 2, Compt rend Acad d sc June 13 1921 p 1526.

shown the merely approximate nature of the law of surface, in tests made with various animals and at various temperatures. The law is strictly applicable only at a certain external temperature characteristic for each animal species, in which conditions of heat production and heat expenditure required to produce equilibrium are also characteristic. At the specific temperature, the total heat loss due to various physical conditions is equivalent to the heat derived from the basal metabolism. Evidently, then, sweeping application of the surface law to all animal species must produce inexact findings.

Benedict has recently revived Voit's theory that basal heat loss is proportional to the total nitrogen of the organism, rather than to its surface. For normal organisms, the conclusions of Lapicque and of Benedict may perhaps be harmonized by a relation possibly existing between the cutaneous surface and the protoplasmic mass of the body. Apart from such restrictions, however, surface is undoubtedly the fundamental element permitting scientific estimation of the basal metabolism, or work, as proved by comparison with results derived from analyses of the respiratory gases. While analytic methods of this kind have been highly perfected, methods and formulas for estimating the body surface are yet debatable, because direct measurements involve much labor and difficulty, and have been rarely made. The various empiric formulas available differ considerably.

Direct measurements of the body surface have utilized three main methods. The first, employing geometric figures traced on the skin, was used by Meeh,⁶ Fubini and Ronchi,⁷ Bouchard,⁸ Letulle and Pompilian,⁹ and Lassablière.¹⁰ In the second process, the body surface is calculated by finding the total area of paper, tin foil or similar material required to cover the surface of the body, or by weighing the material so employed. Funke¹¹ adopted this method for the first time, sticking squares of paper of known area on the skin of a cadaver. Lissauer,¹² Variot and Saint Albin,¹³ the Du Bois¹⁴ brothers and others have

6 Meeh Oberflächenmassungen des menschlichen Körpers, Ztschr f Biol 15 425, 1879

7 Fubini and Ronchi Ueber die perspiration der CO₂ beim Menschen, Moleschotts Untersuchungen, 3, Naturlehre, 1881

8 Bouchard Compt rend Acad d sc, 1897, p 845, Traité de pathologie générale, Paris, 3 200-384, 1900

9 Letulle and Pompilian Bull Soc d'hyg aliment, 1906, p 708

10 Lassablière Compt rend Soc de biol, 1910, p 339

11 Funke Moleschotts Unters, 2, Naturlehre 4 36, 1858

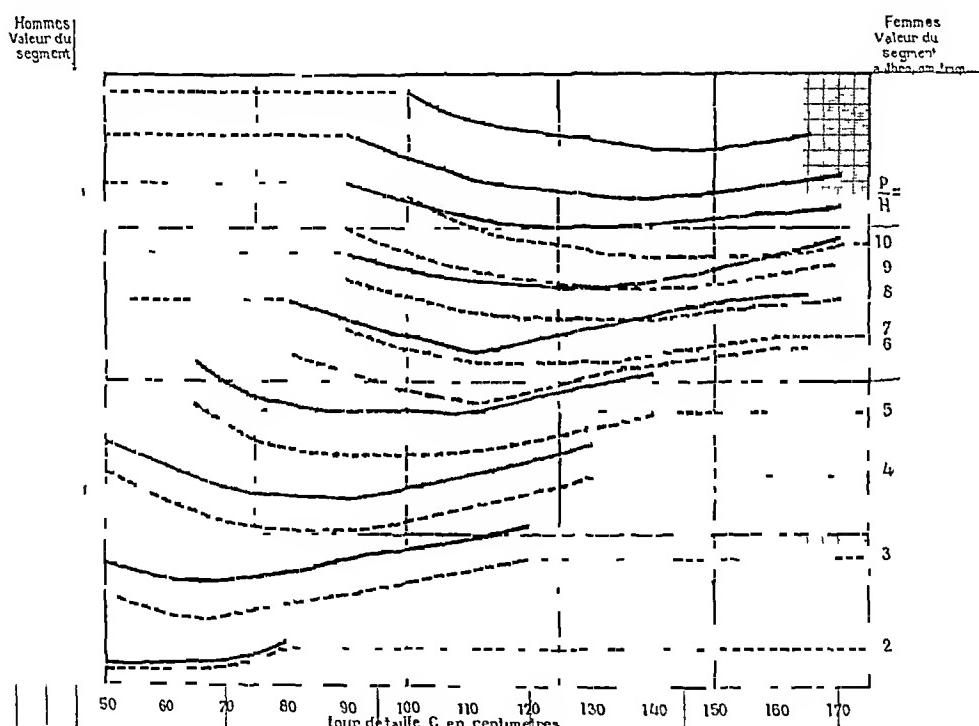
12 Lissauer Oberflächenmassungen an Sauglingen und ihre Bedeutung für Nahrungbedarf, Jahrb f Kinderh, 1902, p 392

13 Variot and Saint Albin Bull Soc de pédiat de Paris 5 307, 1903

14 Du Bois, D., and Du Bois, E. The Surface of the Body, Arch Int Med 17 863 (June) 1916

employed it. The third process, in which the surface of adhesive bandages applied to the body is estimated, has been chiefly employed by Bergonié and Sigalas.

Other ingenious methods have been devised. Roussy traces figures on the skin, measuring them by means of two small rollers placed at the ends of an axle bearing a revolution counter. The number of revolutions made by the rollers is supposedly proportional to the surface over which they travel. This method is fairly exact. D'Aisonval converts his subject into a Leyden jar, measuring the quantity of electricity



Abacus for measuring the human body

required to charge the body surface. Utilizing measurements made in six adults and ten children, Meeh has established an empiric formula based on the mathematical relation according to which the surfaces of similar solids are proportional to their volumes as raised to the two-thirds power, or the cube root of the square of the volumes concerned. In this case, volume is represented by weight. By this method, Meeh determined the constant 12.312, applicable to adults, and another constant, 11.9, for use with children. These constants multiplied by the cube root of the square of the body weight should supply the body surface. When compared with direct measurements, Meeh's method proves to involve error sometimes reaching 33 per cent.

Minute review of all the studies made on the subject is scarcely necessary. The conception and technic originated by Bouchard, however, are fundamental and merit special attention. His critical discussions show the large error produced when body weight constitutes the sole criterion, such error maximally reaching 33 per cent. Bouchard also shows that estimates based only on height and weight may cause error of 15 per cent, and proves still further that the error is very small with formulas utilizing the fundamental constant constituted by the anthropometric segment in association with the girth, or circumferential measurement as made at the level of the umbilicus by tailors. The anthropometric segment consists of the ratio of the weight, expressed in kilograms, to the height, expressed in decimeters. It is thus equivalent to the average weight per decimeter of the subject's height.

The discussion and conclusions contained within the present paper are based on some eighty measurements made directly on persons varying greatly in size. The method employed was the laborious but exact one of triangulation. Bouchard's successors seem very imperfectly acquainted with his masterly work, the Du Bois brothers and their followers accepting formulas which Bouchard has proved incorrect by actual figures. The Du Bois brothers base their weight-height formula on five direct measurements and on certain hypothetic estimates. They assert that Bouchard's methods are unduly complicated. It is intended here to show that Bouchard's formulas may be readily utilized in the construction of an abacus, or graph, that is very simple and practical.

Bouchard's¹⁵ formulas for men and women, as indicated by Broca,¹⁶ may be expressed in the form:

$$S = ACH + B \frac{P}{C} + DH \sqrt[2]{\frac{P}{314H}}$$

In this equation, A , B and D are constants. C represents the girth, or circumferential measurement of the abdomen, expressed in centimeters, H , the height in decimeters, and P , the weight in kilograms. If the foregoing equation is simplified by dividing its terms by H , its equivalent is the following:

$$\frac{S}{H} = aC + b \frac{1}{C} + d$$

a , b and d are values expressing the ratio of the weight to the height. In other words, they solely represent functions of the relation $\frac{\text{Weight}}{\text{Height}}$. The proportion $\frac{S}{H}$ represents the surface of the anthropometric segment. The values of a , b and d , deducible from Bouchard's formulas, are graphically indicated by Broca.¹⁶

15 Bouchard Compt rend Acad d sc 124 848 (April 20) 1897

16 Broca, Andre Precis de physique medicale, pp 47 and 48

The abacus, or graph, here presented has been constructed from the values thus shown in the foregoing. Its curves, or tracings, show the surface of the anthropometric segment, or $\frac{\text{Weight}}{\text{Height}}$ relation, as employed in connection with the girth, C . For utilizing the graph, the weight-height ratio $\frac{\text{Weight}}{\text{Height}}$ must be ascertained, weight being expressed in kilograms and height in decimeters. The girth, C , is stated in centimeters. Its value in the given case is sought on the abscissa. At the point corresponding to this value, a perpendicular is erected and continued upward until it meets the curve corresponding to the given $\frac{\text{Weight}}{\text{Height}}$ ratio. This point of intersection, projected on the ordinate for men or for women, as the case may be, gives a reading which expresses the $\frac{\text{Surface}}{\text{Height}}$ ratio, or surface of the anthropometric segment. The surface, S , is then easily calculated by multiplying the quotient representing the ratio by the given height. This total surface is stated in square decimeters.

The graph may be used easily and rapidly. It is hoped that it may supply exactness for estimating metabolism, and without being more complicated than the less accurate devices of the kind already existing. The curves are particularly interesting because they show that anthropometric segments possess minimal circumferences. If the circumference diminish, the surface increases and the ratio $\frac{\text{Weight}}{\text{Height}}$ is maintained only through compensation afforded by increased development of the limbs, or by some malformation. If the circumference increase, the anthropometric segment represents that one corresponding to a lesser body height, the condition present being one of obesity. Since the minimal surface corresponds to the minimal basal metabolism, or condition fundamental for providing the maximal output of energy, a physiologic relation, or canon, exists between the girth, or abdominal circumference, and the anthropometric segment. This physiologic canon suggests, and may be interestingly compared with, the esthetic canon of proportions devised by Leonardo da Vinci for the correct pictorial or sculptural representation of the human figure.

The flattening of the curves in the graph shows that the physiologic limits are somewhat elastic for moderate anthropometric segments. For small segments weighing less than 2 kg per segment, physiologic conditions cease to exist, the subject presenting a malacic state. For segments weighing 6 kg each, a limit beyond which the subject becomes obese, the corresponding physiologic girth is 110 cm. In other words, the canon is normal and physiologic under these conditions. Above and below the circumference of 110 cm, surface increases rapidly, and obesity appears. With anthropometric segments heavier than 6 kg each, the physiologic canon is annihilated, obesity exists, and the conditions present are pathologic.

For terminating this paper, nothing could be more appropriate than the expression made use of by Bouchard in closing his work on general pathology

The exposition of all this has been much prolonged. Still more time has been required for conceiving and executing it. The object of so much time and trouble has been to save time and trouble for those who wish to undertake such studies. The result may perhaps be identical with the object

BLOOD VOLUME

II A COMPARISON BETWEEN TOTAL BLOOD VOLUMES DETERMINED BY PLASMA VOLUME METHODS AND BY A NEW CORPUSCLE VOLUME METHOD *

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The method of measuring total blood volume by determining the degree of dilution of the transfused corpuscles among the corpuscles of the recipient, previously described,¹ has been applied to cases of secondary anemia, primary anemia, and hemorrhage resulting from operation, the results obtained are compared with the data already on record derived by the use of vital red in similar groups of cases. Since, as has been shown, this method is based on a determination of corpuscle content, a comparison of the results obtained by it with those obtained by a method in which the whole blood volume is calculated from a determined plasma volume is of interest because of its bearing on the problem of the uniformity of distribution of the red corpuscles in the circulation.

The means of measuring plasma volume are numerous. The most satisfactory is the injection of a substance, soluble in the plasma, and the subsequent determination of its degree of dilution. Among the substances used for injection are tetanus antitoxin, gum acacia, hemoglobin and various dyes, but the only considerable amount of clinical data on blood volume has been collected by the use of the dye method, introduced by Keith, Rowntree and Geraghty.² The results obtained by the various methods are, in general, in agreement. There are only two methods for measuring the corpuscle volume of the blood, aside from that introduced in this study. One of these involves the death of the animal, and consists of bleeding and washing out the hemoglobin, this is open to the objection that all the hemoglobin may not be removed. The other, which consists of the measurement of the degree of dilution of carbon monoxide in the hemoglobin contained in the body, is open to the objection that the hemoglobin in the muscles may also take part.

* From the Mayo Foundation

1 Ashby, Winifred Blood Volume, I, A Method for Determining Whole Blood Volume, Based on the Circulating Corpuscle Volume, Arch Int Med

2 Keith, N M, Rowntree, L G, and Geraghty, J T A Method for the Determination of Plasma and Blood Volume, Arch Int Med **16** 547-576 (Oct) 1915

in the dilution of the known amount of carbon monoxid resulting in too high an estimate for the blood corpuscle content. Both methods, however, on calculation of the whole blood volume from the corpuscle volume, give lower values (7 per cent) than are obtained by a calculation of the whole blood volume from the plasma volume.

The greater blood volumes obtained by the determination of plasma volume have been explained on the basis of appreciable loss of the injected substance, soluble in the plasma, before complete mixing has taken place. Lamson and Rosenthal,³ who have studied the initial changes which take place in the dilution of vital red after injection, find irregularities which, on the assumption of a constant volume during the time of examination, they attribute to irregularities in the relative degree of mixing and rate of disappearance from the circulation, and consider that there is indication that mixing is not complete before appreciable elimination takes place. Whipple,⁴ on the other hand, with much reason, calls attention to the wide range in the physical and chemical properties of the substances used for the test, and the similarity of the results obtained with them, arguing that if there were an appreciable loss before complete mixing took place, it should be markedly different with these very dissimilar substances, and should cause a greater difference in results. Whipple⁴ considers that the methods of measuring plasma volume give correct results, as does the measurement of corpuscle volume by carbon monoxid, and that the discrepancy between the whole blood volumes calculated from each is due to an uneven distribution in the corpuscles during the course of their circulation, with the result that the hematocrit reading of a sample of blood taken from the vein fails to give an average relationship between corpuscle and plasma. To meet the condition which the relative findings of the two methods would necessitate, a larger proportion of corpuscles must be present in the vessels from which the blood specimens for the hematocrit readings are taken than elsewhere. Whipple offers the suggestion that this relationship is brought about by the presence of a larger proportion of "clear space" as the blood passes into the smaller vessels and capillaries. Krogh,⁵ however, as a result of direct observation of blood in the process of flow through the capillaries, does not consider that this would be a factor. As a matter of fact, counts made on the blood taken from the

³ Lamson, P. D., and Rosenthal, S. M. The Inadequacy of Our Present Blood Volume Methods, *Am J Physiol* **63** 358-367 (Jan.) 1923.

⁴ Arnold, H. R., Carrier, E. B., Smith, H. P., and Whipple, G. H. Blood Volume Studies, V, The Carbon Monoxid Method Its Accuracy and Limitations, *Am J Physiol* **56** 313-360 (June) 1921.

⁵ Krogh, August. *The Anatomy and Physiology of the Capillaries*, New Haven, Yale University Press, 1922.

ear, simultaneously with that from the basilar vein, will be found to be equal, or the count of the blood from the ear will be greater. Since the blood from the ear is derived largely from small vessels and capillaries, this finding does not support the explanation of the discrepancy between the two methods. The work of Scott⁶ also argues in favor of an evenness of distribution of the corpuscles in the circulation.

The method for determining blood volume described in the first article of this series¹ consists of the injection of unlike group corpuscles by transfusion, and their subsequent separation from the recipient's corpuscles by means of a serum which agglutinates the recipient's corpuscles. With data on the number of corpuscles injected, the degree of dilution may be determined. Assuming that the transfused corpuscles mix evenly with the native corpuscles and follow the distribution of the latter, the method is based on corpuscle content. Therefore, if there should be any irregularity in the distribution of the corpuscles in the circulation, the error, by this method, should be in the opposite direction to that which would occur with a method based on plasma volume determination. Although the method is technically not highly accurate, it has the advantage, because of the great stability of the unlike group corpuscles, of being free from any question as to whether mixing is complete before appreciable elimination takes place. It is also free from the error which is intrinsic to the carbon monoxide method, owing to the presence of the hemoglobin containing tissues outside the circulation.

The technic described¹ has been followed, except that determinations have been made from blood taken from an ear puncture instead of from a venipuncture. The greater part of the data given here was collected incidentally to a study of the rate of destruction of transfused blood, the advisability of using blood from the vein was not at the time recognized. As the error due to using blood from the ear would be in the direction of too high a count, it will, when it occurs, have caused too small a blood volume. It has apparently not been a factor of any importance as the volumes obtained have proved to be large as compared with results obtained with the carbon monoxide method. At the time when the greater part of this work was done, vital red was not available, and a simultaneous use of other methods was not feasible. Except for two simultaneous tests, the comparison of the results obtained by this method and by the method which measures the plasma volume and calculates the whole volume from it, depends on a comparison of the results obtained in similar groups of cases.

⁶ Scott, F. H. Interchange of Fluid in Blood and Tissue Spaces, *Am J Physiol* 44:298 (Oct.) 1917.

In Table 1 are given the results of blood volume determinations by my method in a series of cases of anemia other than pernicious anemia. The results are given in terms of cubic centimeters for each kilogram of body weight on the day of transfusion, and also a few days later, when a readjustment after the transfusion may have taken place. The amount of blood transfused for each kilogram of body weight also is given. In seven cases, between 80 and 85 cc for each kilogram of body weight was found. These volumes were usually maintained after transfusion. The volumes are equivalent to the lower volumes found in normal subjects by the vital red method, and reported by Keith,

TABLE 1—*Blood Volume of Patients with Secondary Anemia After a Single Transfusion*

Case	Age	Sex*	Red Cell Count	Blood, Cc for Each Kilogram of Body Weight	Blood, Cc Transfused for Each Kilogram of Body Weight	Days After Transfusion	Diagnosis
9	33	♀	3.96	96	11	0	Pelvic tumor (second transfusion)
18	35	♂	8.4	84	9	0	Septic teeth, tonsillitis
27	46	♀	3.63	62	6	0	Ovarian tumor (obese)
				52		4	
30	27	♀	3.19	81	4	1	Splenic anemia
				81		6	
53	39	♀	4.47	81	9	0	Exophthalmic goiter, color index 0.4
				85		4	
66	62	♂	3.46	80	6	0	Banti's disease with ascites
99	17	♂	4.73	104	11	1	Malaria
				104		28	
101		♀	3.46	58	8	1	Uterine fibromas, constant bleeding
117		♂	1.99	85	6	0	Transfusion ten days after posterior gastro-enterostomy
				82		3	
118	13	♂	1.85	104	14	0	Hemolytic jaundice
65	11	♂	1.99	98	13	0	Lymphatic leukemia
				140		3	
				185		9	
39	55	♂	3.12	81	7	0	Myelogenous leukemia
115	33	♀	5.13	57†		0	Secondary anemia, septic, not rational

* In this table, ♂ indicates male, ♀ female.

† Low volume maintained.

Rowntree and Geraghty. From calculations based on the actual blood volume, the change in the red cell count resulting from transfusion, and the number of corpuscles transfused, which data will be given later,⁷ it appeared that, in many cases, a greater increase in volume occurred than could be accounted for by the amount of blood transfused. It would seem probable that, in cases of secondary anemia, transfusion tends to establish a normal blood volume. In a case of malaria and in one in which the patient had received a previous transfusion, the higher volumes of 104 and 96 cc for each kilogram of body weight were found. Tests on two children gave values of 104 and 98, which adjusted

⁷ Ashby, Winifred. Blood Volume, III, Apparent Changes in Blood Volume Induced by Transfusion, and Their Bearing on Methods of Determining Blood Volume by Means of the Degree of Change in a Constituent of the Blood, Following Transfusion of a Known Amount of That Constituent, Arch Int Med 35: 641 (May) 1925.

to 140 c.c. for each kilogram of body weight. Low values of 62, adjusting after four days to 52, and of 58 and 57 were found in a very obese woman, a woman with constantly bleeding fibroids, and in a woman with septic anemia who was irrational.

On the whole, these figures for blood volume are definitely of the same order as those obtained with vital red, by the use of which a comparatively large number of determinations have been made on a similar group of cases. In the series of Keith, Rowntree and Geaghty, a miscellaneous group, five of which showed a reduced cell count gave the

TABLE 2—*Blood Volumes of Patients Receiving Transfusions for Primary Anemia*

Case	Age	Sex*	Weight in Kilograms	Red Cell Count	Blood, C.c. for Each Kilogram of Body Weight	Blood, C.c. Transfused for Each Kilogram of Body Weight	Days After Transfusion	Number of Previous Transfusions in Series
20	53	♂	83.2		62 62	4	0 3	0
23	55	♂	66.6	1.23 1.09	71 71	6	0 4	0
26	42	♂	70.5		72	7	1	0
43	49	♂	73.6	1.95	62	5	1	0
45	44	♂	68.2	1.39	60	7	2	0
54	44	♂	66.0		69	8	0	0
57	63	♂	71.3	1.54 1.55	69 55 52	7	3 0	0
59	52	♀	67.7 (obese)	1.88 2.03	49 39	7	0 4	0
60	36	♂	61.0	2.46	63	8	0	1
61	42	♂	66.1	2.40 1.70	71 56	7	4 0	0
68	36	♀	37.3	2.13 1.60	78 65	13	0 3	
70	62	♂	54.4	1.02 1.28	54 73	9	0 1	0
94	55	♂	76.0	2.40 2.38	91 66	6	0 4	2
97	42	♂	70.5	1.89 2.19	75 98	6	0 1	0
112	63	♂	63.0		87 2.29 2.57	6	0 6 8	4
210	51	♀	45.4	3.06 3.19	84 77	11	1 5	0
43	49	♂	69.1	2.39	85	6	0	2

* In this table, ♂ indicates male, ♀ female.

following volumes 93, 88, 84, 80, 92, 84, 114, 96, 96 and 91. In two cases of extreme secondary anemia, in which the red cell counts were 1,070,000 and 1,500,000, respectively, the blood volume for each kilogram of body weight was 73 and 75 c.c., while, in a case of malnutrition, it was 74. In a more recent series, Keith⁸ has reported a volume of 67 c.c. for each kilogram of body weight, and Bock⁹ reports, for seven miscellaneous cases with an average cell count of 3,900,000, an average

8 Keith, N. M. The Total Circulating Volume of Blood and Plasma in Cases of Chronic Anemia and Leukemia, Am. J. M. Sc. **165**: 174-184 (Feb.) 1923.

9 Bock, A. V. The Constancy of the Volume of the Blood Plasma, Arch. Int. Med. **27**: 83-101 (Jan.) 1921.

volume of 71 cc for each kilogram of body weight. In three cases of leukemia, Keith⁸ finds values varying from 96 to 131, 100 to 123, 87 to 102, and, in a case of Banti's disease, a volume of 98 cc for each kilogram of body weight was found.

Blood volumes in seventeen cases of pernicious anemia are given in Table 2. Most of the patients received a series of three or more transfusions of 500 cc each, at intervals of about a week. Some of the patients received transfusions for the first time, others had had a previous series of transfusions. The average volume of twelve patients who received either their first transfusion, or the first of the present

TABLE 3.—Blood Volumes Found After Postoperative Transfusions

Case 22	Age 32	Sex* ♂	Red Cell Count	Days After Opera- tion	Blood, Cc for Each Kilogram of Body Weight		Operation
					4	4	
			4 30	11	85	92	
				22	22	88	
38	32	♀	2 95	6	5	44	Removal of multiple lipoma,
			2 92	10	9	46	Von Recklinghausen's dis-
			3 67	21	20	50	ease, moderately obese
			3 07	24	23	57	
			3 75	27	26	62	
			4 00	30	29	72	
			4 29	33	32	70	
			4 11	35	34	63	
50	50	♂	4 40	19	12	81	Choledochostomy and chole-
			4 50	27	20	98	cystectomy
			4 67	29	22	88	
				31	24	90	
63	33	♂	4 93	0	0	39	Nephrectomy
			3 12	2	2	66	
			4 42	20	20	91	
84	46	♀	3 45	0	0	29	Carcinoma of the kidney,
			2 83	1	1	36	nephrectomy, obese
			3 72	8	8	88	
			4 20	12	12	82	
114		♀	3 63	4	4	45	
			3 49	6	6	52	
			3 14	11	11	76	
			3 47	15	15	81	

* In this table, ♂ indicates male, ♀ female.

series, was 65.8, the average red cell count was 1.84. Bock, in a series of seven patients with pernicious anemia, found an average volume of 57 (extremes of 43 to 73), but as the average cell count of these patients was 1.6, they were evidently in a poorer condition than those of the group tested by my method. Keith⁸ has reported the blood volume of a series of thirteen patients on some of whom multiple determinations were made. The average of the first volume determinations made on each patient is 79.8 cc for each kilogram of body weight, and of the corresponding red cell counts, 1.76. These values for blood volume are higher than those found, in my series, for the first transfusion, the patients were presumably under treatment, while my figure of 65.8 was obtained from patients at the beginning of treatment. In four cases

cited in Table 2, in which the unlike group transfusion from which the blood volume determination was made was not the first in the series, the blood volume for each kilogram of body weight was 63, 95, 96 and 85 cc. Taking into consideration the probable difference in the condition of the patients, the figures for blood volume in my series of patients with pernicious anemia would seem to agree very well with those found by Keith and Bock with the use of vital red.

In the eight cases on record in which the carbon monoxide method was used to determine blood volume in patients with pernicious anemia the range as determined by Smith,⁴ 47 to 117, also is comparable to that found by the vital red method. In cases of pernicious anemia, there is apparently not the discrepancy between the method of estimating blood volume by determining the serum volume and the method of estimating it from a determination of the corpuscle volume by the carbon monoxide method which appears in normal cases.

In Table 3 are given blood volume changes which have been found on recovery from operation with hemorrhage, requiring transfusion. Comparable series are given by Keith¹⁰ and by Robertson and Bock,¹¹ in their studies of wounded soldiers. These data on the blood volume are somewhat inaccurate, as the transfusions were given in emergency, but are reasonably reliable.

The blood volumes finally established are comparable to those found by the vital red method for normal subjects, and for the recovered soldiers of Keith, following intravenous treatment. The progress of the establishment is also similar to that found by Keith. The blood volume of the moderately obese patient with Von Recklinghausen's disease did not return to normal, although the patient recovered satisfactorily. This may have been due to a peculiarity of the patient, or to an inadequate estimate of the number of corpuscles transfused. The very low blood volume of 39, found in Case 33, and of 29, found in the case of the obese woman, would seem lower than is probable. As the blood specimens from which the blood volume determinations were made were taken from the ear, it is likely, in view of the great discrepancy between the ear and vein count found by Cannon¹² in shock, that these counts were unduly high, and consequently gave too low a blood volume reading, although Lee¹³ reports as low as 30 per cent normal blood volume in wound shock.

10 Keith, N. M. Blood Volume Changes in Wound Shock and Primary Hemorrhage, Medical Research Council, 1919, Special Report No. 27.

11 Robertson, O. H., and Bock, A. V. Blood Volume in Wounded Soldiers, J. Exper. Med. 29: 155 (Feb.) 1919.

12 Cannon, W. B., Fraser, J., and Hooper, A. N. Some Alterations in Distribution and Character of Blood in Shock and Hemorrhage, J. A. M. A. 70: 526-531 (Feb. 23) 1918.

13 Lee, R. I. Field Observations on Blood Volume in Wound Hemorrhage and Shock, Am. J. M. Sc. 158: 570-576 (Oct.) 1919.

Simultaneous tests were made by my method and by the vital red method on a patient with pernicious anemia, five days after transfusion had been given. The determination was made from blood taken from the vein. In this instance, the counts of blood specimens taken from the vein and from the ear were equal. The volume for the whole blood by the vital red method was 78.8, by my method, 77. Of course no great importance can be attached to the close agreement of this single set of parallel determinations, the main evidence lies in the general agreement between blood volumes found by my method and those found by the use of vital red in the same type of case.

Simultaneous tests made on a patient with lymphatic leukemia, having a high white count, 445,000, did not give equal results. The volume by my method was 66, while by the vital red method, it was 87.9. The white cells, which are unagglutinable, were distinguished by staining the preparation with brilliant cresyl blue. Many of the white cells, however, did not stain sufficiently to make them easily distinguishable from the red cells, and it is probable that many of them were counted as reds, resulting in too high a count and too low a blood volume. The white counts in the two cases of leukemia, quoted in Table 1, were not high enough to be considered a factor.

Tables 1 and 2 include all cases of secondary anemia and primary anemia on which complete data for determining the blood volume were available, that is to say, in which it was possible to get satisfactorily checking and duplicate counts of the unagglutinable corpuscles in the patient's blood before and after transfusion, and of the blood transfused, and in which I had an accurate record of the amount of blood given. There were, however, many other cases in which all these data were not complete, but in which a fairly reliable estimate could be made. The volume estimates for these cases agree with those given.

SUMMARY

Total blood volumes estimated by a new method, based on the measurement of the corpuscle content of the circulation following transfusion with blood of an unlike group, are compared with those estimated from plasma volume determinations. By the new method, the transfused corpuscles, after becoming uniformly mixed with the native corpuscles, would follow the distribution of the latter, and any error in the estimation of the total blood volume, owing to an irregularity in the distribution of the corpuscles in the circulation, would be in an opposite direction to the error possible by the plasma volume method, as in any given specimen of blood that was not representative the relative plasma content and corpuscle content, which respectively determine the whole blood volume estimate by each method would have errors that would vary inversely.

The values for whole blood obtained by the new method are in agreement with those obtained by the vital red method, and in disagreement with the whole blood volumes of normal subjects obtained by the carbon monoxid method. The agreement of the results obtained by these two methods would argue against any irregularity in the distribution of the blood corpuscles in the system, and would suggest that there is some factor inherent in the carbon monoxid method which has caused the low results obtained in normal subjects.

The agreement of the data obtained by the new method, in which there is apparently no question of loss of the injected substance, the dilution of which is to be tested during the time necessary for complete mixing in the circulation, with the data obtained by the method involving the injection of a dye, which is comparatively rapidly eliminated, would indicate that the technic of the dye methods involves no appreciable loss before mixing is complete.

BLOOD VOLUME

III APPARENT CHANGES IN BLOOD VOLUME INDUCED BY TRANSFUSION, AND THEIR BEARING ON METHODS OF DETERMINING BLOOD VOLUME BY MEANS OF THE DEGREE OF CHANGE IN A CONSTITUENT OF THE BLOOD, FOLLOWING TRANSFUSION OF A KNOWN AMOUNT OF THAT CONSTITUENT¹

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During the course of a study of the immediate effect of transfusion on the blood count, certain data have appeared which seem to indicate that, besides the change in volume due directly to the transfusion, changes in the total volume occur, due to increase or decrease in the recipient's plasma. These apparent changes in the blood volume may take place within a short time after transfusion without inconvenience to the patient and may be either increases or decreases. In certain patients, these changes do not occur, especially in those whose blood is comparatively normal. If they really are blood volume changes, they would be a source of error to any method of determining blood volume, which is dependent on the injection of a known amount of some constituent already present in the blood, and the subsequent measurement of the increase in that constituent, because they would vitiate the initial reading.

Although there is a tendency for blood volume to be constant, this is due to the mobility of the blood volume rather than to its rigidity. The rapidity with which the blood plasma in healthy animals increases, to compensate for loss of blood, is a point of evidence, as also is the tendency for the blood to recover its original volume after transfusion, as has been reported by Keith, who has, in certain instances, found that blood volume was no more increased after transfusion than before. The mobility of the blood volume in response to change in conditions produced by external factors has recently been demonstrated in studies by Barbour¹ on the effect of heat and cold, and possibly also by the rather wide diurnal variation in the hemoglobin content, described by Dreyer².

Although the mechanism of blood volume control is by no means fully understood, Krogh's conception of it would seem to offer a good

¹ From the Mayo Foundation

1 Barbour, H. G. Heat Regulation and Water Exchange, I, Effects of Hot and Cold Baths Upon Blood Concentration and Brain Volume Regulation in Dogs, *Am J Physiol* **67** 366-377 (Jan) 1924

2 Dreyer, G., Bazett, H. C., and Pierce, H. F. Diurnal Variations in the Hemoglobin Content of the Blood, *Lancet* **2** 588-591 (Sept 18) 1920

working hypothesis. The point of exchange of fluids is the capillary wall, which is permeable to water and to crystalloids,³ but generally not to colloids. Since crystalloids readily pass through the capillary walls, they have no permanent part in the maintenance of blood volume. This function is performed by the slight osmotic pressure of the colloids. The capillaries of the intestinal tract Krogh regards as being more permeable than those of the rest of the body, and as the location where colloids in a finer state of subdivision are lost. Krogh has correlated the height of an animal with the degree of dispersion of the colloids of its blood, and the consequent osmotic pressure which they are capable of exerting. He finds that the blood serum of a horse, for instance, which, because of the height of the column of fluid in its vessels, is exposed to a higher filtration pressure than that of the rabbit, not only contains more serum protein than that of the rabbit, but its serum proteins are in a finer state of division. Blood volume, then, would be influenced by the state of subdivision of the colloids of the blood, as well as by their amount. A minimal amount of work has been done on the quantitative protein content of the blood serum in normal and pathologic conditions, but our knowledge of its physical state is practically nil.

It would seem quite possible for two human blood serums to exert considerably different osmotic pressures. This would seem especially probable if one serum were derived from a subject in a state of health, and the other from one who was in need of a blood transfusion. The latter serum might not only have a different quantitative content of protein, but also a different qualitative content. It is probable that the ratio between serum globulin and serum albumin would be different in the two bloods, and it is possible that the state of aggregation of the particles of a single constituent might be different. Accordingly, the added serum might exert either greater or less osmotic pressure than the serum of the recipient, in which event it would upset the balance between the tissue fluids and the blood, and cause an exchange of water and salts. It also is conceivable that the added serum might, because of higher or lower alkalinity or other factors, produce a change in the recipient's serum proteins, thus causing a change in their osmotic pressure, and a consequent exchange of fluid with the tissues.

I believe it is probable that some such mechanism will explain the data which follow, although it must be admitted that other explanations than that of change of volume are possible. After a transfusion of unlike blood has been given and the necessary data obtained for deter-

³ Krogh, A. *The Anatomy and Physiology of the Capillaries*, New Haven, Yale University Press 1922.

mining the blood volume, it has often been noted that either the blood count of the recipient was not raised, even though it had originally been considerably lower than that of the blood transfused, or it was not raised sufficiently to account for the even distribution of all the transfused corpuscles through the circulation of the recipient. On the other hand, the blood count has sometimes been raised too much to account for the amount of blood given. The low count following transfusion is explicable, either on the basis of an exchange of fluid from the tissues to the blood serum, or by an immediate destruction of some of the recipient's own corpuscles. The high count may be explained either by an immediate destruction of some of the transfused corpuscles, giving a higher blood volume estimate than is correct, or by a loss of fluid from blood serum to tissues. The exchange of fluid seems to me the more probable explanation.

Counts were taken before and after transfusion, usually soon after the patient had been returned to his room. The volume of the blood after transfusion was calculated by the method already given, and from the blood volume, the patient's blood count after transfusion, and the amount and count of the transfused blood, a value for the count of the patient's blood before transfusion was calculated, on the basis of a comparison of this calculated count, and the actual count before transfusion, an estimate of the change in blood volume, aside from that due to fluid added by the transfusion, was made. The method of calculation was as follows: the number of corpuscles added by the transfusion, $C_t \times V_t$, C_t and V_t being the count and volume of the transfused blood, divided by V , the patient's blood volume after transfusion, gives the number of corpuscles for each cubic millimeter added by the transfusion. This subtracted from C , the count of the recipient's blood after transfusion, gives the count of the recipient's corpuscles at the volume of the blood after transfusion. This multiplied by $\frac{V}{V - V_t}$ should give the count before transfusion, provided no destruction of corpuscles nor change in fluid content other than that made by the transfusion has taken place. On the assumption that any difference in the observed and calculated count is due to an exchange of fluid between tissue and serum, the original blood volume is obtained from the formula,

$$V^o = (V - V_t) \times \frac{C^e}{C^b},$$

in which C^e and C^b are the calculated and actual blood counts before transfusion. $(V - V_t) - V^o$ will be the change due to exchange of fluid. From these formulas, the apparent changes auxiliary to the transfusion have been calculated in a series of patients with secondary and primary anemia (Tables 1 and 2).

Of the cases of secondary anemia (Table 1), in three there was no change in the count that could be attributed to change in volume that was not accounted for by the transfusion. In two there was a slight increase, and in three an increase in volume beyond that added by the

TABLE 1—*Immediate Blood Volume Readjustments Apparently Produced by Transfusion in Patients with Secondary Anemia*

Case	Red Cell Count				Blood Volume						
	Before Transfusion		Days After Transfusion	Pre previous Transfusions	After Transfusion	Kilogram of Body Weight	Calculated Volume Before Transfusion	C c for Each Kilogram of Body Weight	C c for Each Kilogram of Body Weight	Amount Transfused, C c	Change*
	Actual	Estimated									
9	4.05	4.07	3.96	0	0	4,340	96	3,840	85	500	0
193	3.17	3.43	3.76	0		1,035	82	820	65	275	-60
53	4.59	4.50	4.47	0	0	4,250	81	3,750	72	500	0
							85				
118	1.56	1.42	1.85	0	0	3,430	105	2,700	82	440	290
283	4.82	4.48	4.54	0	2	3,600	67	2,850	53	540	210
66	3.58	3.36	3.46	0	0	6,000	80	5,220	70	430	350
117	1.98	1.74	1.99	0	0	3,820	85	3,120	69	280	420
						76					
27	4.00	3.63	3.54	0	0	3,925	61	3,480	49	425	445
					5	52					

* Unaccounted for by transfusion.

TABLE 2—*Immediate Blood Volume Readjustments Produced by Transfusion in Patients with Primary Anemia*

Case	Red Cell Count				Blood Volume							Change Unac- ounted for by Trans- fusion	
	Before Transfusion		Days After Transfusion	Pre previous Transfusions	After Transfusion	Kilogram of Body Weight	C c for Each Kilogram of Body Weight	Esti- mated Original Volume	C c for Each Kilogram of Body Weight	Amount Transfused, C c			
	Actual	Estimated											
57	1.17	1.15	1.54	0	0	3,900	55	3,450	48	450	0		
			1.65	6			55						
59	1.33	1.43	1.88	0	0	3,300	48	3,040	45	475	-215		
			1.77	1			45						
61	1.48	1.23	1.70	0	0	3,700	56	2,660	40	500	+560		
			6				62						
97	1.90	1.59	1.89	0	0	5,350	75	4,100	58	440	+810		
			2.19	1			96						
70	0.61	0.28	1.02	0	0	2,900	54	1,100	21	500	+1,300		
			1.28	1			73						
71*	0.66	0.28	0.87	0	0	4,300		1,610		490	+2,810		
			1.07	4		5,100							
212	1.16	0.56	1.10	0	0	3,000		1,270		400	+1,330		
			1.64	1		2,620							
94	2.04	2.24	2.40	0	2	7,250		7,300		460	-560		
			2.38	4		5,020							
205	1.43	1.95			6								
212	1.63	1.97	2.35	1	1	3,520	49†	4,870	59	440	-1,120		
			2.27	1		4,540				500	-830		

* Marked edema which disappeared after transfusion.
† Edema

transfusion, which was about equal to the amount of blood transfused. The three cases in which there was a greater increase on addition of normal serum were a case of Banti's disease with ascites, a case of obesity and low blood volume, and a case in which posterior gastro-enterostomy had been performed ten days before, the patient's blood count being 1,990,000, and the blood serum in all probability depleted

In the series of patients with pernicious anemia, the blood counts indicated a greater exchange of fluid between tissue and blood. This, I believe, is more probably due to a greater abnormality of the serum, although the explanation is also plausible that there is a greater tendency for the native corpuscles to be destroyed. It is possible that in some cases, Case 71 for instance, both factors may have come into play. Of

TABLE 3.—*Change in Blood Count and Indicated Fluid Exchange Following First Transfusion of a Series, Compared with That Occurring Following Subsequent Transfusions*

CASE	Count Before Transfusion	Difference	Diagnosis
Patients Receiving First Transfusion			
1	4,600,000	-260,000	Secondary anemia
2	1,890,000	+280,000	Primary anemia
3	1,370,000	-40,000	Primary anemia
4	1,190,000	+260,000	Primary anemia
5	2,870,000	-290,000	Malignancy
6	2,180,000	+370,000	Primary anemia
7	4,500,000	-50,000	Jaundice
8	4,580,000	-8,000	Malignancy
9	2,700,000	-220,000	Primary anemia
Av for cases with positive change	1,590,000	+300,000	
Patients Receiving Second Transfusion			
10	1,730,000	+460,000	Primary anemia
11	3,440,000	+300,000	Jaundice
12	2,420,000	+400,000	Secondary anemia
13	1,490,000	-30,000	Primary anemia
14	1,160,000	+620,000	Primary anemia
15	1,290,000	+360,000	Primary anemia
16	1,640,000	+420,000	Primary anemia
17	3,070,000	-460,000	Primary anemia
18	1,550,000	+360,000	Primary anemia
Av for cases with positive change	1,890,000	+430,000	
Patients Receiving Third to Fifth Transfusion			
19	2,430,000	+210,000	Primary anemia
20	2,390,000	+200,000	Primary anemia
21	1,820,000	+520,000	Primary anemia
22	1,300,000	+330,000	Primary anemia
23	1,910,000	+570,000	Primary anemia
24	1,970,000	+530,000	Primary anemia
25	2,000,000	-60,000	Primary anemia
26	1,700,000	+300,000	Primary anemia
27	2,270,000	+570,000	Primary anemia
28	3,030,000	+270,000	Secondary anemia
Av for cases with positive change	2,090,000	+390,000	

Theoretical Increase in the Blood Count after Transfusion Calculated on the Basis of a 500 cc Transfusion at a Count of 4,440,000 Red Cells is Compared with the Actual Increase and Interpreted as Change in Volume

Transfusion	Actual Increase	Estimated Increase	Difference	Fluid Exchange, C c
Average Blood Volume of 3,800 C c Assumed				
First	300,000	380,000	-70,000	+
Second	430,000	330,000	+100,000	-160
Third to fifth	390,000	310,000	+80,000	-120
Average Blood Volume of 4,200 C c Assumed				
First	300,000	340,000	-40,000	+
Second	430,000	300,000	+130,000	-230
Third to fifth	390,000	280,000	+110,000	-180
Average Blood Volume of 500,000 C c Assumed				
First	300,000	280,000	+20,000	-60
Second	420,000	250,000	+180,000	-390
Third to fifth	390,000	230,000	+1,660,000	-330

a series of seven cases of first transfusions, there was no indication of a change in volume in one, and in another, practically none, in five there was an apparent increase in volume besides that added by transfusion, which ranged from 560 to 2,810 c.c. In three patients who had received previous transfusions, there was an apparent loss of fluid, in two of these, the determinations were not made until the day following the transfusion, and in the meantime it is possible that the bone marrow may have put out new cells, and so caused the unexplained increase, which gave the appearance of decreased blood volume.

Further data which are pertinent to the question were obtained from patients receiving transfusions of blood of the same group. In these cases blood volume estimates could not be made, but a comparison of the counts before and after transfusion offers evidence. For several days, counts were made on all patients referred for transfusion, and the data were classified according to the number of transfusions which had been previously given (Table 3). Of the nine first transfusions, six caused a reduction in the blood count, of these, three were given to patients with secondary anemia whose counts before transfusion were as high as, or higher than, the count of the blood transfused. The recipients, however, in three instances had low initial blood counts. In the three instances in which the transfusion raised the count, the average increase was 303,000 corpuscles for each cubic millimeter, on an initial average blood count of 1,590,000. Of nine second transfusions, only two caused a decrease in the initial count of the blood, and seven an increase, which averaged 430,000 corpuscles for each cubic millimeter, on an average initial count of 1,880,000. Of ten patients who were receiving from the third to fifth transfusion, only one had a lower count after the transfusion than before, the average increase in the eight other counts was 390,000, on an average initial count of 2,090,000. Without blood volume data, the significance of the counts which increased has been estimated on the basis of an assumed range of blood volumes, which would seem to cover the probabilities.

In the second paper of this series, the average blood volume of a series of patients with pernicious anemia, receiving blood transfusion for the first time, was 4,260 c.c. The average volume in a series reported by Keith,⁴ some of whose patients had probably had several transfusions, was 4,360 c.c. As the average blood percentage by volume was lower, in proportion to the figure for the average blood volume, in my series than in Keith's, it seemed possible that in mine there may have been a larger proportion of tall subjects, therefore, to be on the safe side, I

⁴ Keith N M. The Total Circulating Volume of Blood and Plasma in Cases of Chronic Anemia and Leukemia, Am J M Sc **165** 174-184 (Feb) 1923

have taken 3,800 as the first blood volume. This would be equivalent to 6.4 per cent of the body weight of a subject weighing 130 pounds (59 kg.), too low an estimate for the average blood volume of the patients receiving their second to fifth transfusions. I have also assumed the blood volumes 4,200 and 5,000 cc., which would be respectively 7.1 and 8.5 per cent of the body weight of a subject weighing 130 pounds (59 kg.). The latter would seem the more probable estimate for the average blood volume of the patients who had received more than two transfusions. In the estimate of the probable count of the transfused blood, I used the average of a series of counts on citrated blood, taken in the same amount and prepared in the same operating room. This count was 4,440,000 corpuscles for each cubic millimeter. Transfusions of 500 cc. were given in all cases.

In considering these cases in which there was an increase in the count resulting from transfusion, it was assumed that the initial average count of the patient's corpuscles was diluted by transfusion to $\frac{V - 500}{V}$ times the average initial count, V being the average blood volume after transfusion. It was assumed that the transfused blood was diluted after transfusion to $4,440,000 \times \frac{500}{V}$. The two figures added are the count after transfusion, provided no change in volume has taken place, and the difference between this and the initial count is the increase that should take place in the count on the basis of the assumed blood volume. The blood volume change was obtained by multiplying V by the factor, calculated blood count divided by actual blood count, and subtracting the product from V . There is obviously a slight error in these formulas, but it is of no importance in this connection. The calculations are appended to Table 3. With all three blood volume estimates, the calculations show that after the second to the fifth transfusions the corpuscle counts were greater than would be accounted for by the blood transfused, and indicated a passage of fluid from plasma to tissues. For the first transfusion, the two lower blood volume estimates give calculated increases which, in comparison with the actual increase, indicate a passage of fluid from tissue to blood, and even for the highest blood volume estimate, which is undoubtedly too high for a first transfusion, the estimated and actual counts are practically equal. This series shows a marked difference in tendency of direction of change in volume between the first transfusion of a series and the later ones. The transfusions were spaced about a week apart.

Since the blood from which all these data are derived was obtained by puncture of the ear, there was the possibility that, with the freer flow after transfusion, the lower count obtained might merely be due to the technic of taking the blood. This point was controlled in one

instance in which the Lewisohn blood volume method was compared with that of Ashby. The percentage of corpuscles in the blood taken from the vein of the patient before transfusion was 23.4 by the hematocrit reading, fifteen minutes after the transfusion, it was 23.1, the reading of the transfused blood was 43.6 per cent. Four hundred eighty cubic centimeters were given. The patient's blood volume after transfusion was estimated from the count of the unagglutinable corpuscles to be 4,450 cc., or 8.2 per cent of her body weight. The case was one of secondary anemia, there was no transfusion reaction. The blood from the basilic vein showed, in this instance, the same degree of decrease in corpuscle content after transfusion as the ear puncture revealed in the cases already cited.

SUMMARY AND CONCLUSION

Following the first transfusion, changes are likely to occur in the recipient's blood count so that destruction of the recipient's corpuscles or an addition of fluid from the tissues is observed within half an hour after the beginning of transfusion. As these changes are not associated with hematuria or any tendency toward reaction, and as they are apparently more apt to occur in patients whose condition is such that a reduced protein content might be expected, I consider it probable that they are due to change in volume caused by a higher osmotic pressure of the serum introduced. In patients who have been transfused recently, the chances that this apparent increase in blood volume will occur following a second transfusion are much diminished, and in the majority of cases there is indication that an exchange of fluid from blood to tissue occurs on transfusion. Among my studies of second and third transfusions, there was only one in which I had all the necessary data for determining this exchange, and in that study there was evidence of it. In the study of the change of count in a larger series of like group transfusions in which blood volume could not be determined, but in which a probable range of blood volume could be safely estimated, there was found, following most second to fifth transfusions, excess in the increase of the corpuscle count, which would indicate a passage of fluid from blood to tissue, while, following the first transfusions, the change in count indicated a passage of fluid from tissue to blood. Keith,⁵ who uses the vital red method, has also reported observations of no increase in volume after transfusion.

In accounting for the difference between the osmotic pressure of the patient's and donor's bloods, one would expect to find, as one of the factors, a difference in protein content, either quantitative or qualitative,

⁵ Keith, N. M. Blood Volume Changes in Wound Shock and Primary Hemorrhage, Medical Research Council, 1919, Special Report No. 27.

such that a difference in the number of molecular aggregates might occur. Wells,⁶ in his summary of the literature on the serum protein content in patients with pernicious anemia, says that the serum proteins are reduced, the decrease being in the serum globulin Peters and Rubnitz,⁷ on the other hand, report a higher protein content than normal in the serum of patients with severe anemia. So, apparently, both conditions are possible. That plasma volume may be abnormally high in patients with pernicious anemia has been reported by Keith. In line with the idea that the apparent tendency to exchange of fluid from tissue to blood, on repeated transfusion, is due to increase in osmotic pressure from increase in protein content would be my own data (fourth paper of this series), which seem to indicate that the blood volume of patients with pernicious anemia is usually greater following later transfusions than at the first transfusion of a series, even when there is no great change in the total cell volume. A series of transfusions apparently tends to stimulate an increase in plasma volume, probably owing to increase in protein content. It would seem probable that the protein content might be stimulated to an excess of increase, such that, after a series of transfusions, the difference between the osmotic pressure of the donor's and patient's plasma might be reversed.

If these discrepancies between the counts of the patient's blood before and after transfusion are in reality due to change in blood volume, they would be a source of error in any method for determining blood volume, which utilized the change of concentration of any constituent of the blood by transfusion, if, on the other hand, they are due to corpuscle destruction, they would still be a source of error to any method which utilized the change in concentration of the corpuscle content resulting from transfusion.

Although the data have been so collected that the changes are known to occur within half an hour after transfusion, it is very possible that they are of almost immediate occurrence. These changes bear no relationship to the occurrence of transfusion reactions.

6 Wells, H G Chemical Pathology, Ed 3, Philadelphia, W B Saunders Company

7 Peters, A W, and Rubnitz, A S Observations on the Chemical Pathology of the Blood in Pernicious Anemia and Other Severe Anemias, Arch Int Med **26** 561-569 (Nov) 1920

ANATOMIC FINDINGS IN ESSENTIAL HYPERTENSION^{*}

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The concept of essential hypertension includes those cases of chronic hypertension which neither clinically nor anatomically can be demonstrated to have evolved from antecedent inflammatory disease of the kidneys or from urinary obstruction. The clinical picture of essential hypertension is, as a rule, quite distinctive, and has become widely known, in recent years, through the publications of Huchard,¹ Janeway,² Allbutt,³ Volhard⁴ and others, in their respective countries. As a result of these studies, it is now possible to diagnose essential hypertension with a fair degree of certainty in the large majority of cases. But we are occasionally confronted at necropsy by a secondary (i.e. postnephritic) contracted kidney, despite the fact that the clinical features of the case gave no indication that the hypertension was associated with inflammatory disease of the kidneys. Because of such rather exceptional cases, essential hypertension cannot be unequivocally defined by the absence of clinical evidence of nephritis or of urinary obstruction, and it is necessary to add the word "anatomically" to the definition to prevent the inclusion of those cases of nephritis in which the identity is first revealed at the postmortem table. This definition is very seriously defective in that it defines the disease solely by exclusion, but, in our present ignorance of the causes of hypertension in general, it does not seem feasible to define essential hypertension in any more satisfactory way. Nevertheless, the consideration of essential hypertension as a distinct nosologic entity seems fully justified, both from a clinical and, as will be discussed below, from an anatomic point of view.

Essential hypertension, thus defined, is very much more common than chronic hypertension associated with inflammatory disease of the kidney. Of eighty-two cases of chronic hypertension coming to necropsy at the Montefiore Hospital, seventy-two, or 88 per cent, were instances of

* From the Medical Division of the Montefiore Hospital

1 Huchard Traité clinique des maladies du coeur et de l'aorte, Paris, 1 45-125, 1899

2 Janeway, T C A Clinical Study of Hypertensive Cardiovascular Disease, Arch Int Med 12 755-798 (Dec) 1913

3 Allbutt Diseases of the Arteries, Including Angina Pectoris, London, 1 378-454, 1915

4 Volhard and Fahr Die Brightsche Nierenkrankheit, Berlin, 1914, pp 210-246

essential hypertension. However, it should be stated that the patients in the Montefiore Hospital are largely sufferers from chronic diseases, and that, therefore, the proportion of true nephritis is probably somewhat smaller than in the usual hospital service.

In the present paper, we desire to report on the anatomic findings in these seventy-two cases of essential hypertension and their interpretation.

ARTERIOLAR LESIONS

Cases of clinically typical essential hypertension in which neither renal nor arteriolar lesions of consequence were found at the necropsy have been described by various authors.⁵ But it is evidently rather rare for such a case to come to necropsy, and one must agree with Hueck⁶ that the existence of hypertension for more than a few weeks can usually be read in the arterial walls. Every one of our seventy-two cases of essential hypertension showed more or less marked but always clearly defined arteriolar changes. It is of great interest that the arteriolar lesions so constantly accompanying essential hypertension are essentially identical in the various organs, and of equal significance that, as will be seen below, they have a very characteristic distribution. To this well defined lesion of the arterioles, the term arteriolosclerosis has been aptly applied. As has long been known, arteriolosclerosis occurs most frequently and most markedly in the kidney, and it may, therefore, be best to describe first the evolution of the typical lesion in that organ.

The histologic picture of arteriolosclerosis develops somewhat differently in the smallest arterioles, the vasa afferentia, than in the next larger vessels, the vasa interlobulares. In the afferent arterioles, the first change noted is a deposition of so-called hyaline substance directly under the endothelium. Fortunate longitudinal sections show that the hyalinization does not occur uniformly along the course of the vas afferens, but usually begins close to the junction with the glomerular tuft. The highly refractile hyalin appears pink in ordinary hematoxylin-eosin preparations and yellowish-orange in sections stained by van Gieson's method. In the earliest stages, this hyalin is not stained by Sudan III, but later on it quite frequently undergoes fatty change and gives lipoid reactions. Hueck⁶ believes that the hyaline substance is semifluid and, in the early stages at least, causes little increase of resistance to the flow of blood. In the larger interlobular arterioles, the first change observed is apparently hyperplasia of the internal elastic membrane with reduplication and the formation of multiple lamellae.

5 Pal Ueber Herzhypertrophie und Hypertonie, Med Klin 15 662, 1919
Von Monakow Blutdrucksteigerung und Niere, Deutsch Arch f klin Med 133 129, 1920

6 Hueck Anatomisches zur Frage nach Wesen und Ursache der Arteriolosclerose, Munchen med Wechschr 67 835, 1920

(Jores' hyperplastic type of intimal thickening) The hyperplastic elastic tissue undergoes regressive changes with the appearance of lipoid and hyaline substance and reactive proliferation of the neighboring connective tissue, gradually resulting in marked narrowing of the lumen which may slowly go on to complete obliteration In the earliest stages of the process in both afferent and interlobular arterioles, the media do not present any marked changes, but a progressive atrophy of the muscle cells with fatty and hyaline change then sets in and, finally, fibrous replacement As far back as 1868, Johnson⁷ described hypertrophy of the media as a characteristic in granular kidney and most current textbooks contain the same statement, but, as a matter of fact, one finds in arteriosclerosis a gradual and progressive degenerative atrophy of the medial muscle with replacement fibrosis This is in a certain contrast to the larger vessels in essential hypertension, as well as to the arterioles in true nephritis, in which I have occasionally observed an apparent medial hypertrophy The latter is, however, difficult to ascertain with certainty, as Jores⁸ pointed out, because of deceptive appearances caused by postmortem contraction The progressive intimal thickening just described naturally leads to a progressive narrowing of the lumen But to this there is a noteworthy exception, first described by Loehlein,⁹ which I have repeatedly been able to confirm In the early stages of the hyaline change in the vasa afferentia, these vessels are often tremendously dilated at their entrance into the glomerular tuft, warranting Loehlein's description of the dilatation as "lakelike" The dilatation also may involve the first divisions of the vas afferens, so that in longitudinal sections a Y-like figure is seen, often packed with red cells Only the terminal part of the vas afferens is thus dilated, and it may follow on a marked constriction

It is, of course, of primary importance whether these arteriolar lesions, found in practically all cases of essential hypertension, also occur in patients with normal blood pressure In vasa interlobulares, reduplication of the internal elastic lamina is often seen beginning with the fourth decade, or even earlier, and usually attains a considerable extent in elderly people, though not approaching that seen in cases of chronic hypertension of the same age Hyalinization of the vasa afferentia to a slight degree is often seen at a later period of life, but I have not seen marked hyalinization of the afferent arterioles in a case with normal tension (except in the vicinity of inflammatory lesions, e.g., pyonephrotic

⁷ Johnson On Certain Points in the Anatomy and Pathology of Bright's Disease, Tr Med -Chir Soc **51** 57, 1868

⁸ Jores Ueber die Arteriosclerose der kleinen Organarterien, Virchows Arch f path Anat **178** 374, 1904

⁹ Loehlein Ueber Schrumpfnieren, Beitr z path Anat u z allg Path **63** 570, 1917

lesions) In the spleen, on the contrary, well marked and progressive hyalinization is physiologic and sets in quite early in life Principally, the central arterioles of the malpighian bodies are involved Thus, Herxheimer¹⁰ found, in an investigation of 1,100 spleens, that hyalinization was present in 15 per cent of those under 10 years of age, in more than half of those between 30 and 40, and in three-quarters of the patients over 60 The hyaline substance found in the splenic arterioles of people with normal blood pressure is apparently identical with that in cases of hypertension, it also often undergoes fatty change The physiologic occurrence of hyaline change in the splenic arterioles often renders it difficult to decide whether or not changes observed in these vessels in a case of hypertension have any correlation with the high blood pressure

DISTRIBUTION OF THE ARTERIOLAR LESIONS

It has been known since Gull and Sutton's¹¹ pioneer communication that arteriolosclerosis is not always confined to the arterioles of the kidney, in fact, it is quite common usage to speak of "generalized arteriosclerosis" of the smaller radicals, implying the existence of a system disease of the arterioles of the body Most investigators have confined their examination of the smaller vessels in essential hypertension to those of the kidney But the arterioles in other organs have also received some attention Thus, Jores⁸ found that the lesions of the small arterioles which he described as the pathogenetic agent in the primary contracted kidney also were to be found in the arterioles of other organs Munzer,¹² in a number of publications, has championed Gull and Sutton's half century old view that nonnephritic hypertension is secondary to a generalized arteriocapillary fibrosis, to explain the frequent absence of any visible changes in the arterioles throughout the body, he invokes the inadequacy of our present histologic methods This view has been disputed by Fahr,¹³ who maintains the predominant rôle of the lesions of the renal arterioles, and points out that the small vessels of the skin, voluntary muscles and intestines are very rarely involved Hasenfeld¹⁴ and others have claimed that essential hypertension is due to sclerosis of the arterioles of the splanchnic area In

10 Herxheimer Ueber das Verhalten der kleinen Gefäesse der Milz, Berl klin Wchnschr **54** 82, 1917

11 Gull and Sutton On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease, Tr Med -Chir Soc **55** 273, 1872

12 Munzer, E Gefäesssklerosen, Wien Arch f inn Med **21** (Dec) 1920

13 Fahr Ueber die Beziehungen von Arteriolensklerose, Hypertonie, und Herzhypertrophie, Virchows Arch f path Anat **239** 41, 1922

14 Hasenfeld and Hirsch Ueber die Herzhypertrophie bei Arteriosklerose, Deutsch Arch f klin Med **59** 193, 1897

an extensive investigation, Evans¹⁵ found that the small vessels of the spleen are involved about as often as those of the kidney, while the minute branches of the coronary arteries are never affected.

In view of these differences of opinion as to the distribution of the arteriolar lesions associated with hypertension, we have systematically examined the arterioles of the various organs in the seventy-two cases of essential hypertension on which this study is based. The findings are summarized in the following table. It is to be emphasized that this table has reference only to the lesions found in the minute arterioles, i.e., those corresponding in size to the *vasa interlobulares* and *vasa afferentia* of the kidney. For lack of any more adequate method, we have expressed the grade of the arteriolar lesions by the symbols N for normal, 1 plus, 2 plus, 3 plus and 4 plus. A dash means that the organ was not investigated. The word normal has, of course, been used in a relative sense, taking into consideration those changes which physiologically occur in the arterioles of the various organs with advancing years, and which are, therefore, not correlated with the hypertension. The hyalinization that occurs normally in the arterioles of the spleen (discussed in the foregoing) renders particularly difficult the investigation of the smaller radicals of that organ, and the findings in the splenic arterioles tabulated below must therefore be taken with some reserve.

The cutaneous arterioles were examined in seventeen cases and those of the voluntary muscles in fifteen, in no instance was arteriolosclerosis noted.

If Table 1 is studied, it is seen that the organs fall into three groups with regard to the involvement of their arterioles in essential hypertension.

1 *Kidney*—In essential hypertension, the arterioles of this organ are involved much more frequently and far more intensely than those of any other portion of the body. In every one of the seventy-two cases examined, the renal arterioles were affected. Moreover, in almost every instance, the severity of the arteriolar lesions in the kidney greatly exceeded that in any other organ. In ten of the cases, the arterioles of the kidney were the only ones affected. However, in several cases, the involvement of the renal arterioles was only slight, these will be discussed in connection with the interpretation of the lesion.

2 *Spleen, Pancreas, Liver and Brain*—In cases of essential hypertension, arteriolosclerosis is a common finding in these organs. Involvement of the splenic arterioles occurs in about two thirds of the cases, the pancreatic in about half, the hepatic in less than a third, and the

15 Evans A Contribution to the Study of Arteriosclerosis, Quart J Med
14 215, 1920

TABLE 1.—Distribution and Intensity of Arteriolar Lesions in Essential Hypertension

Blood Pressure								Pancreas	Gastro-Intestinal Tract			Supra-renals
Necropsy No	Age	Sys tolic	Dias tolic	Kidneys	Heart	Lung	Liver	Brain	Stomach	Small Intestine	Large Intestine	N
1	46	240	150	+++	N	N	N	+	-	-	-	N
2	54	228	100	++++	N	N	N	-	-	-	-	+
3	70	170	100	++++	N	N	N	-	-	-	-	+
4	70	210	94	++++	N	N	N	-	-	-	-	+
5	75	205		++	N	N	N	-	-	-	-	+
6	63	180	110	++++	N	N	N	-	-	-	-	+
7	59	210	118	++++	N	N	N	-	-	-	-	+
8	50	High		++++	N	N	N	-	-	-	-	+
9	53	160	100	++	N	N	N	-	-	-	-	+
10	54	195	130	++++	N	N	N	-	-	-	-	+
11	50	190	130	++++	N	N	N	-	-	-	-	+
12	83	210	160	++++	N	N	N	-	-	-	-	+
13	59	140	100	+++	N	N	N	-	-	-	-	+
14	53	210	100	+++	N	N	N	-	-	-	-	+
15	56	210	98	+++	N	N	N	-	-	-	-	+
16	70	170	102	+++	N	N	N	-	-	-	-	+
17	64	186	110	++	N	N	N	-	-	-	-	+
18	56	214	114	++	N	N	N	-	-	-	-	+
19	75	170	95	++	N	N	N	-	-	-	-	+
20	80	255	165	++	N	N	N	-	-	-	-	+
21	70	264	145	++	N	N	N	-	-	-	-	+
22	55	240	110	++	N	N	N	-	-	-	-	+
23	60	180	100	++	N	N	N	-	-	-	-	+
24	55	200	114	++	N	N	N	-	-	-	-	+
25	62	170	94	++	N	N	N	-	-	-	-	+
26	56	265	130	++	N	N	N	-	-	-	-	+
27	60	160	88	++	N	N	N	-	-	-	-	+
28	62	180	100	++	N	N	N	-	-	-	-	+
29	72	170	100	++	N	N	N	-	-	-	-	+
30	54	225	100	++	N	N	N	-	-	-	-	+
31	56	270	130	++	N	N	N	-	-	-	-	+
32	40	175	120	++	N	N	N	-	-	-	-	+
33	60	150	100	++	N	N	N	-	-	-	-	+
34	60	200		++	N	N	N	-	-	-	-	+
35	87	204	103	++	N	N	N	-	-	-	-	+
36	52	238	140	++	N	N	N	-	-	-	-	+
37	75	194	120	++	N	N	N	-	-	-	-	+
38	60	240	135	++	N	N	N	-	-	-	-	+
39	58	140	95	++	N	N	N	-	-	-	-	+
40	65	195	105	++	N	N	N	-	-	-	-	+
41	83	220	110	++	N	N	N	-	-	-	-	+
42	54	180	135	++	N	N	N	-	-	-	-	+
43	70	232	130	++	N	N	N	-	-	-	-	+
44	52	180	110	++	N	N	N	-	-	-	-	+
45	71	190	92	++	N	N	N	-	-	-	-	+
46	65	190	92	++	N	N	N	-	-	-	-	+
47	69	210	110	++	N	N	N	-	-	-	-	+
48	73	High		++	N	N	N	-	-	-	-	+
49	72	170	90	++	N	N	N	-	-	-	-	+
50	63	210	130	++	N	N	N	-	-	-	-	+
51	60	140	110	++	N	N	N	-	-	-	-	+
52	69	180	95	++	N	N	N	-	-	-	-	+
53	58	202	128	++	N	N	N	-	-	-	-	+
54	69	150	110	++	N	N	N	-	-	-	-	+
55	96	140	90	++	N	N	N	-	-	-	-	+
56	53	190	90	++	N	N	N	-	-	-	-	+
57	60	204	130	++	N	N	N	-	-	-	-	+
58	52	275	165	++	N	N	N	-	-	-	-	+
59	56	230	125	++	N	N	N	-	-	-	-	+
60	63	200	125	++	N	N	N	-	-	-	-	+
61	62	165	120	++	N	N	N	-	-	-	-	+
62	60	High		++	N	N	N	-	-	-	-	+
63	72	162	100	++	N	N	N	-	-	-	-	+
64	75	160	80	++	N	N	N	-	-	-	-	+
65	78	188	96	++	N	N	N	-	-	-	-	+
66	72	High		++	N	N	N	-	-	-	-	+
67	46	180		++	N	N	N	-	-	-	-	+
68	62	150	90	++	N	N	N	-	-	-	-	+
69	47	260	130	++	N	N	N	-	-	-	-	+
70	34	225	145	++	N	N	N	-	-	-	-	+
71	71	190	92	++	N	N	N	-	-	-	-	+
72	57	175	106	++	N	N	N	-	-	-	-	+
Total cases examined				72	68	70	68	70	68	31	34	59
Arteriolar lesions present				72	2	0*	45	21	23	6	3	17

* These patients had mitral stenosis and the lesions of the pulmonary arterioles are to be attributed to the valvular lesion and not to the hypertension, they are, therefore, not considered in the totals.

cerebral in about one fifth of the cases. But the lesion usually is not very marked, rarely being even nearly as intense or diffuse as in the kidney. There is no constancy about the involvement of these organs, any one or more of them may be involved in a given case. The most marked arteriolar changes in these organs are found only in association with a very advanced process in the renal arterioles. Another organ in which arteriolosclerosis is quite often found is the suprarenal gland, which was involved in seventeen of sixty cases. Here, the arteriolar thickening is best seen in the connective tissue capsule. But considerable hyaline change of the arterioles of this organ is not uncommon in persons with normal arterial tension.

3 Skin, Skeletal Muscles, Myocardium, Lung, Gastro-Intestinal Tract and Thyroid.—In these organs, the lesions of arteriolosclerosis are found only rarely and then to only an insignificant extent. Thickening of the smaller arterioles of the lung is occasionally seen when the hypertension is accompanied by mitral stenosis, an association which is not uncommon, but is then attributable to the valvular lesion and consequent increase of pressure in the lesser circuit. I have not seen any clearly defined example of the lesion in the voluntary muscles, or more than minimal involvement of the arterioles within the myocardium, and that only twice in sixty-eight cases. In two instances, slight intimal thickening of arterioles in the pericardial tissues was seen without any corresponding change in the vessels of the heart muscle proper. The stomach and intestines are only very uncommonly involved by arteriolosclerosis, and then the lesion is very slight. I have not found any basis for the view that essential hypertension is due to sclerosis of the splanchnic vessels. These findings are in essential agreement with those of previous authors who have examined various organs. Thus, Evans¹⁵ has noted the rarity of lesions of the smaller arterioles (which he terms diffuse hyperplastic sclerosis instead of the term arteriolosclerosis used here) in the heart muscle and gastro-intestinal tract, Fahr,¹³ the rarety in the skin, voluntary muscles and gastro-intestinal tract, and Watanabe¹⁶ found thickening of the small arterioles of the skin in only six of 116 cases.

In the testis, prostate and pituitary gland, which were examined in a small number of instances, arteriolosclerosis was not noted. The ovary and uterus were not studied because regressive changes of somewhat different histologic appearance are frequent findings in association with menstruation, pregnancy and senile involution. I had no opportunity for anatomic study of the minute arterioles of the retina, this would have

¹⁶ Watanabe, S. Ueber die Arteriosklerose der Hautgefaesse, Schweiz med Wochenschr **51** 780 (Aug 25) 1921

been desirable as it has recently been shown by O'Hare and Walker¹⁷ that the retinal arterioles of a size to be seen ophthalmoscopically are usually thickened in essential hypertension.

It is of interest to compare the incidence of arteriosclerosis in the various organs with the frequency of senile arteriosclerosis of the large vessels in these organs.

The figures for arteriosclerosis in Table 2 are taken from Brooks'¹⁸ investigation of 400 cases. He gives no figures for the vessels of the extremities, but the great frequency of senile arteriosclerotic changes (including here medial calcification) in the radials, tibials and other large arteries of the extremities is a matter of everyday observation. On the other hand, it was seen above that arteriolosclerosis is exceedingly rare in the tissues making up the extremities, i.e., muscle and skin.

This comparison of the incidence of lesions of the large and small vessels in the various organs of the body thus reveals no parallelism in their distribution. On the contrary, a sharp divergence is to be noted, arteriolosclerosis invariably affecting the kidney, with the spleen,

TABLE 2.—Incidence of Arteriosclerosis and Arteriolosclerosis in Various Organs

	Arteriosclerosis, per Cent	Arteriolosclerosis, per Cent
	High	0
Extremities		
Heart	78	3
Brain	36	19
Kidney	23	100
Pancreas	20	49
Liver	12	80
Spleen	10	66
Lung	5	0

pancreas and liver next in order of frequency, while large vessel atherosclerosis has its sites of predilection in the extremities, heart and brain. Neither lesion occurs in the arteries of the lesser circulation in correlation with essential hypertension.

The study of the distribution of the arterial lesions thus affords a point of view from which it seems very probable that different factors enter into the pathogenesis of arteriolosclerosis than are concerned in the production of atherosclerosis of the large vessels. This is confirmed by certain other evidence.

1. Arteriolosclerosis of any considerable degree is constantly accompanied by essential hypertension, while senile arteriosclerosis apparently has little correlation with hypertension.

2. The age incidence of arteriolosclerosis is somewhat different from that of large vessel sclerosis. The maximum age incidence of arterio-

17 O'Hare, J. P., and Walker, W. G.: Arteriosclerosis and Hypertension, Arch. Int. Med. 33: 343 (March) 1924.

18 Brooks: A Preliminary Study of Visceral Arteriosclerosis, Am. J. M. Sc. 131: 778, 1906.

sclerosis is that of essential hypertension, i.e., middle life, while large vessel lesions continue to increase in frequency with advancing age, being most common in very old persons.

3 It has been shown by the Aschoff school that the large vessel lesions can be produced—in herbivora, at least—by derangements of lipid metabolism. In uncomplicated experiments of this nature, the small vessels are not affected.

SIGNIFICANCE OF THE ARTERIOLAR LESIONS

The interpretation of the arteriolar lesions resolves itself into the old question of the relation they bear to the hypertension of which they are a constant accompaniment. Half a century ago, two theories were formulated, each of which still has its advocates.

1 Gull and Sutton's¹¹ view¹⁹ that the disease of the arterioles is primary and causes the hypertension by mechanically narrowing the peripheral stream bed, thus increasing the peripheral resistance.

2 Johnson's⁷ theory of substances failing of excretion by a primarily diseased kidney causing a spasm of the peripheral arterioles and thus functionally increasing the peripheral resistance. According to this view, the hypertension would be the cause of the arteriolar lesions.

That the hypertension is due to the mechanical increase in resistance caused by organic lesions of the smaller arterioles does not seem possible, in view of the limited arteriolar areas that are thus affected even in the most extensive cases. We have seen that the arteriolar lesions are usually severe only in the kidneys, and that while a few other organs (spleen, liver, pancreas and brain) may be involved to a slight or, at most, to a moderate extent, the great mass of the arterioles of the body, in the striped muscles, skin, gastro-intestinal tract and heart, show practically no lesions. It is well known from physiologic experiments that any increased peripheral resistance in an organ is immediately compensated for by a vasodilatation elsewhere in the body, so that no increase in the general blood pressure occurs. The arteriolosclerosis would have to involve very extensive regions were it to increase mechanically the peripheral resistance by an amount too great to be compensated for elsewhere, i.e., it would have to be a true generalized arteriolosclerosis. But it was shown above that it involves only a small

19 Peculiarly enough, Gull and Sutton did not actually observe the intimal thickening which we now know to be the most striking change in the small vessels. They thought the thickening of the arterioles was due to a "hyalin-fibroid" change in the adventitia. This is shown by their illustrations and their statement (p 283) that "the morbid changes we have observed occur chiefly outside the muscular layer." The error of these brilliant and original observers is readily understood when it is recalled that their histologic methods consisted in the study of frozen sections in which the nuclei were stained by carmin.

fraction of the great arterial periphery, the vast majority of the arterioles are left with an unnarrowsed lumen. In brief, a true generalized arteriolosclerosis does not exist in association with essential hypertension and, therefore, cannot be the cause of the latter.

It was pointed out above that lesions of the arterioles identical in nature with the arteriolosclerosis associated with chronic hypertension are a physiologic accompaniment of advancing years. Hyalinization of the smallest arterioles of the spleen begins to appear quite early in life, in middle-aged people, elastic hyperplasia is found in slightly larger arterioles in various organs, while late in life a slight degree of hyalinization of the vasa afferentia of the kidney can often be observed. These changes are a manifestation of the wear and tear to which the arterioles, the effectors of the never resting vasomotor nerves, are subject with advancing years. The arteriolosclerosis of essential hypertension may rationally be regarded as merely a pathologic exaggeration of these physiologic changes manifesting the tremendously increased strain put on the arterioles by the heightened blood pressure. The exact mechanism by which the increased strain of hypertension causes the arteriolar lesions is evidently complex and as yet totally unexplained; it does not consist solely in the increased blood pressure from within, for in that event the arteriolar lesions would be diffuse and not confined to a few organs, as we have found to be the case. Another of our findings which we have been unable to explain is the markedly atrophic condition of the medial musculature of the diseased arterioles. On the basis of the theory that essential hypertension is caused by increased tonus of the peripheral arterioles—and this is a theory supported by much cogent evidence—one would expect, by analogy with other tubular organs, that the medial musculature would be hypertrophic, as is the elastic tissue. But we have pointed out above that a progressive atrophy is the rule in essential hypertension.

RENAL LESIONS

Though instances of simple chronic hypertension which have not evolved from antecedent inflammatory disease of the kidney are here considered as cases of essential hypertension, nevertheless, renal lesions form an almost constant finding when such cases come to necropsy. The relation of these renal lesions to the high blood pressure has occupied the focal point of all discussions relative to the pathogenesis of the hypertension. It was formerly believed that the renal lesions are the results of a chronic interstitial inflammation, whence the name for these cases of chronic interstitial nephritis, still in common use. But the investigations of Ziegler,²⁰ Jores⁸ and numerous others have demon-

²⁰ Ziegler Ueber die Ursachen der Nierenschrumpfung, Deutsch Arch f klin Med 25 586, 1880

strated beyond cavil that the pathogenetic factor in these cases is the arteriolosclerosis, and that the lesions of the renal parenchyma are secondary to the disease of the minute arterioles. Nevertheless, the Romberg²¹ school and a considerable, though diminishing, number of others still hold that the cause of all persistent hypertension is the renal lesion. The untenability of this view is, I believe, shown by study of the histologic changes in essential hypertension.

As mentioned above, cases have been described by various authors in which chronic arterial hypertension is unaccompanied by any renal lesion. In our series of seventy-two cases, we were not fortunate enough to observe such an instance, but there were several in which maximal hypertension was associated with only minimal renal lesions.

REPORT OF CASES

CASE 1—M. L., a man, aged 52, had a history of progressive cardiac insufficiency, but nothing in it pointing to preceding acute nephritis. The blood pressure was 275 systolic, and 165 diastolic. No evidence of renal insufficiency was seen.

Necropsy was performed. The cause of death was diagnosed as coronary thrombosis. The heart weighed 810 gm., there was great hypertrophy and dilatation, most marked in the left ventricle. The kidneys weighed 370 gm., and were slightly enlarged. The capsule stripped readily, revealing a smooth surface except for a few scattered depressions. Microscopically, an infarct was seen. Some of the vasa interlobulares showed moderate hyperplastic intimal thickening, but most were unaffected. A few of the vasa afferentia showed slight hyalinization. Here and there, a hyaline glomerulus and atrophic tubule were seen, but the parenchyma in general was excellent, the only diffuse change seen being moderate cloudy swelling of the tubular epithelium, obviously recent.

CASE 2—J. S., a woman, aged 58, had a cerebral hemorrhage three months before admission. The systolic blood pressure was 202, the diastolic 128. There was myocardial insufficiency.

Necropsy was performed. The causes of death were diagnosed as bronchopneumonia and pulmonary edema. The heart weighed 400 gm., there was left ventricular hypertrophy and dilatation. The kidneys weighed 310 gm., their surface was smooth. Except for some elastic hyperplasia in the larger arterioles and a few slightly hyaline vasa afferentia, the intimate vasculature of the kidney appeared normal. There were only very few hyaline glomeruli with atrophic tubules, the parenchyma in general revealed no long standing change.

From these cases, it is seen that very marked chronic hypertension may exist in the presence of renal changes consisting solely in slight arteriolosclerosis with consequent obliteration of a very small number of glomeruli and their appertaining tubules. The injury to the renal parenchyma may be so slight that it is necessary to search the sections carefully to discover it. It is known from ablation experiments that about three quarters of the renal parenchyma may be removed without any renal insufficiency manifesting itself. Moreover, the beautiful

²¹ Romberg, Krankheiten des Herzens und der Gefässse, Stuttgart, 1921, p. 582.

experiments of Richards²² have shown that only a fraction of the glomeruli (and presumably also of their tubules) work at the same time. In view of this enormous factor of safety possessed by the kidney, it seems impossible that the destruction of such a vanishingly small proportion of the renal parenchyma as is often found at the necropsy of cases of essential hypertension could, by depressing any of the functions of the kidney, entail such systemic consequences as hypertension.

Another anatomic consideration points in the same direction. The kidney is made up of a large number of functionally equivalent units, each consisting of a glomerulus and a long uriniferous tubule. Each such unit (nephron) is, so to speak, a miniature kidney in itself. Moreover, the vas afferens is a miniature renal artery, for, after emerging from the glomerulus as the vas efferens, it forms the sole or principal blood supply of the corresponding proximal and distal convoluted tubules. In essential hypertension, the injury to the kidney consists in the successive destruction of one such unit (miniature kidney) after another, for when the glomerulus becomes hyalinized as a result of the arteriolosclerotic process in its vas afferens, the corresponding tubule also atrophies. Obliteration of the glomerulus entails atrophy of the corresponding tubule for two reasons:

1. The sole or principal blood supply of the convoluted tubules is furnished by the vas efferens of the corresponding glomerulus.

2. Disuse atrophies the tubular epithelium, which no longer has the glomerular filtrate to work on.

In view of this successive destruction of complete renal units, there can be no question of injury to one of the partial functions of the kidney while the others remain intact. (This could only occur if there were a great difference in the factors of safety for the different partial functions, a view for which I know of no adequate evidence.) There must be, rather, a quantitatively equal reduction in all the functions. In the vast majority of cases of essential hypertension, however, such of the functions of the kidney as we are able to measure are for a long time not appreciably depressed. It does not, therefore, seem justified to hold that any one substance (e.g., one with pressor properties) is retained while those which we can measure are excreted normally.

FINDINGS WHEN ESSENTIAL HYPERTENSION IS COMPLICATED BY RENAL INSUFFICIENCY

Contrary to views widely held prior to the development of adequate methods for studying kidney function, it is now generally appreciated that the large majority of patients suffering from essential hypertension do not develop any significant renal insufficiency. It has been seen, in the foregoing section, that the anatomic findings would not lead us

to expect inadequate renal function, for the lesions in the kidney are focal and not diffuse. The usual causes of death are directly attributable to the increased mechanical strain under which the circulatory apparatus labors (cardiac insufficiency and cerebral vascular insults) or intercurrent diseases. However, in a certain, though small, proportion of cases, the kidney function becomes inadequate. In our seventy-two cases with necropsies, five, or 7 per cent, of the patients died with renal insufficiency. This is a much smaller incidence of uremia than is found in chronic nephritis.

What is the cause of renal insufficiency in this small proportion of cases of essential hypertension, while the vast majority (93 per cent of our series) complete the course of their disease with intact kidney function? This question of the pathogenesis of renal insufficiency in essential hypertension was first systematically attacked on the basis of comparison of the results of modern renal function tests with the postmortem findings by Volhard and Fahr²³ in their well known monograph of 1914. They divided the cases of essential hypertension into two groups:

1 Pure (benign) hypertension without renal insufficiency. In these cases (making up the vast majority of the total), the kidneys exhibit only foci of arteriolosclerotic scarring, while between these scarred areas there is left ample parenchyma to carry on the excretory functions.

2 The combination form (Kombinationsform) or malignant hypertension, in which renal insufficiency is superimposed on a previously existent pure hypertension. In such uremic cases, they found, in addition to the arteriolosclerotic foci, glomerular and other changes which they did not believe could be explained solely as secondary to the mechanical effects of the small vessel sclerosis. The glomerular findings were akin to those noted in cases of acute and subacute nephritis, consisting of proliferation of the epithelium of Bowman's capsule and of the endothelial cells of the glomerular capillaries, slight accumulation of leukocytes in the capillary loops and exudation into the capsular space. These changes they considered as inflammatory in nature and as evidencing the addition of a toxic nephritis to the preexistent arteriolosclerosis. This nephritic addition was held responsible for the onset of renal insufficiency.

While the clinical utility of Volhard and Fahr's division of cases of essential hypertension into two classes depending on the presence or absence of renal insufficiency has been generally recognized, their conception that the onset of uremia is attributable to a superadded nephritis has met with spirited opposition on the part of most pathologic anatomists.

23 Volhard and Fahr. Die Brightsche Nierenkrankheit, Berlin, 1914, p. 80.

(Loehlein,²⁴ Jores²⁴ and Herxheimer²⁵) The latter admit the existence, in a relatively slight degree, of the findings described by Volhard and Fahr, but believe them due solely to the vascular lesions, and do not consider them evidence of the addition of a toxic inflammatory component. In more recent publications, Volhard and Fahr, while maintaining the accuracy of their original observations, have modified their conception of the pathogenesis of the renal insufficiency. Volhard²⁶ now believes the onset of inadequate renal function in a case of essential hypertension to be coincident with the occurrence of a general vasoconstriction, which has among its consequences ischemia of the glomeruli, albuminuric retinitis and the general pallor of the skin which is almost always found in renal insufficiency (even in the absence of anemia) in place of the previous plethoric appearance. Fahr,²⁷ on the contrary, holds that the lesions of the kidney in cases with renal insufficiency are due to an affection of the arterioles different from the arteriolosclerosis found in benign hypertension. This affection he describes as a rapidly progressive necrotizing arteritis of the renal arterioles, which soon impedes the renal circulation sufficiently to cause uremia. He terms the disease malignant sclerosis, in contradistinction to the benign sclerosis of uncomplicated hypertension. I have not been able to find the inflammatory arteriolar changes described by Fahr in essential hypertension with uremia, though such inflammatory changes of the arterioles are occasionally seen in nephritis.

Of the seventy-two cases of essential hypertension given in Table 1, in only five was renal insufficiency present, manifested by nitrogen retention and symptoms of uremia. In four others, there was moderate increase of nonprotein nitrogen in the blood without other clinical evidence of renal insufficiency or symptoms of uremia. Study of the anatomic changes in the seventy-two cases tabulated indicates that instances of essential hypertension with accumulation of nitrogen in the blood are of three varieties, anatomically characterized by

- 1 Coalescence of the arteriolosclerotic foci
- 2 Occurrence of more or less diffuse reactive glomerular changes
- 3 Evidence of cardiac insufficiency

1 *Coalescence of the Arteriolosclerotic Foci*—*A priori*, it would seem that the usual cause of kidney insufficiency in essential hypertension with its accompanying arteriolosclerosis would be the successive obliteration of one area of parenchyma after another till the margin of safety

24 Jores Ueber den pathologischen Umbau von Organen, Virchows Arch f path Anat **221** 14, 1916

25 Herxheimer Ueber die genuine arteriolosklerotische Schrumpfniere, Beitr z path Anat u z allg Path **64** 297, 1918

26 Volhard Der arterielle Hochdruck, Verhandl d deutsch Gesellsch f inn Med **35** 134, 1923

27 Fahr Ueber Nephrosclerose, Virchows Arch f path Anat **226** 119, 1919

has been exceeded. But while this is the usual mechanism in chronic nephritis, in essential hypertension it evidently occurs in only a very small proportion of the cases. In the extensive material reported in their monograph, Volhard and Fahr²⁸ did not see one instance of this type, but mention having been shown such material by Aschoff. In our series, there was one uncomplicated case of this variety, and another case in which both tremendous obliteration of parenchyma and cardiac failure played parts.

CASE 3—D. L., a woman, aged 54, had blood pressure 225 systolic, 100 diastolic. Blood chemistry findings were urea nitrogen, 128, uric acid, 85, creatinin, 41, and sugar, 130 mg per hundred cubic centimeters. Phenolsulphonephthalein excretion after intramuscular injection was less than 5 per cent in two hours. Dilution and concentration tests showed the specific gravity to be fixed at 1.008-1.009. Albuminuric retinitis was present. Necropsy revealed the heart to weigh 680 gm. The finely granular kidneys together weighed only 160 gm. There was extreme arteriosclerosis of the vasa interlobulares and vasa afferentia, which, in many instances, had progressed to complete obliteration of the lumen. Almost all the parenchyma had been obliterated and replaced by cellular connective tissue. Nearly all the glomeruli had been completely hyalinized. There were islands of dilated tubules lined by low epithelium. A few regenerated tubules were seen. The few glomeruli that were not obliterated were hypertrophic and exhibited no proliferative or exudative changes. There was little round cell infiltration.

In the foregoing case, the gradual obliteration of the glomeruli and their appertaining tubules finally progressed so far that compensation by the vicariously functioning remaining units became impossible. In the following case, destruction of the renal parenchyma had not proceeded quite so far, but cardiac failure precipitated the renal insufficiency while there was still a rather small amount of intact kidney tissue.

CASE 4—M. R., a woman, aged 56, had blood pressure 270 systolic, 130 diastolic. The urea nitrogen, on admission, was 19.6, then rose to 48.6 mg per hundred cubic centimeters. Phenolsulphonephthalein excretion was first 9.5 per cent, then diminishing to 2.5, and finally to 0 per cent in two hours. The specific gravity of the urine varied (spontaneously) between 1.013 and 1.016. Albuminuric retinitis was present.

Necropsy was performed. The heart weighed 430 gm. There was marked atherosclerosis of the larger coronary branches, one of which was freshly thrombosed (probably immediate cause of death). There was extensive myomalacia cordis. The red, granular kidneys together weighed 200 gm. There was extreme arteriosclerosis. There were very many hyaline glomeruli and great fibrous replacement of the parenchyma. But there were a considerable number of apparently intact glomeruli which were congested. From the amount of uninjured parenchyma, one would not expect severe renal insufficiency. The onset of the latter was evidently precipitated by cardiac failure, due to the very severe coronary artery disease.

2. Occurrence of Reactive Glomerular Changes.—These are the cases described by Volhard and Fahr (discussed above) as the combination form. The arteriosclerotic process is well marked, but between the

areas of hyalinized glomeruli and atrophic tubules there are considerable portions which have not undergone arteriolosclerotic atrophy. These glomeruli present, to a varying degree, proliferative and exudative changes. Three such cases were included in the foregoing series.

CASE 5—E I, a man, aged 47, known to have had hypertension for two years before admission, complained of headache, weakness and increasing irritability for the last six months. He was irrational when admitted. There was no cyanosis, dyspnea or edema. The blood pressure ranged from 230 systolic, 120 diastolic, to 240 systolic, 170 diastolic. The urea nitrogen was 68.9, later, 89.7, uric acid, 4, and creatinin 4.1 mg per hundred cubic centimeters. The phenolsulphonephthalein output after intramuscular injection was 7 per cent in two hours. Examination of the urine revealed specific gravity, 1.010, a heavy trace of albumin and a few hyaline casts. The concentration test could not be done. Ophthalmoscopic examination was neglected. Soon after admission, the patient went into coma and died, eight days after entrance.

Necropsy was performed. The heart weighed 760 gm, there was marked left ventricular hypertrophy and dilatation. The red, finely granular kidneys weighed 340 gm. There was extreme hyalinization of the vasa afferentia and moderate hyperplastic thickening of the interlobulares. A good many hyaline glomeruli were seen, others showed periglomerular fibrosis. In a few glomeruli, areas of necrosis were seen. In many of the tufts, proliferation of the endothelial cells had occurred so that they appeared rich in nuclei; in these glomeruli, the capillary loops were almost entirely devoid of red cells, being filled, in many instances, with a pink staining amorphous substance. The tubules showed well marked degenerative changes. Interstitial fibrosis was prominent, and there was considerable round cell infiltration.

CASE 6—E F, a woman, aged 34, when operated on for hernia, a year and a half before admission, was told that she had high blood pressure. The chief complaints on admission were dyspnea on exertion and precordial pain and dizziness, both of about a year's duration. There was no history of nephritis, but during her last pregnancy, a year before, she had had some disturbances evidently correlated with the hypertension. On admission, she was somewhat dyspneic and cyanotic. The blood pressure was 208 systolic, 132 diastolic. Albuminuric retinitis was present. When admitted, the renal function was not severely impaired, the phenolsulphonephthalein output (intramuscular injection) was 35 per cent in two hours, and the blood chemistry findings were urea nitrogen, 19.6, and uric acid, 1.8 mg per hundred cubic centimeters. For about a month, her condition seemed somewhat improved, but then she became stuporous and evidence of renal insufficiency appeared, the blood urea nitrogen mounting to 67 mg per hundred cubic centimeters. During this period, a left hemiplegia appeared. She was comatose during the last week of life.

Necropsy was performed. There was a fresh hemorrhage in the region of the right internal capsule. The heart weighed 700 gm, there was very marked hypertrophy and dilatation of the left ventricle. The finely granular kidneys weighed 300 gm. The smaller arterioles showed well marked hyaline-fatty intimal thickening. There was only slight elastic hyperplasia. Only a few glomeruli had been hyalinized. Most of the malpighian corpuscles contained few or no red cells in their loops. In some, considerable proliferation of the nuclei of the tuft was present. The glomerular capsules showed no evidence of epithelial proliferation, but some of them contained pink staining exudate in the capsular space. The tubules showed only slight regressive changes. The arterioles of the pancreas, spleen, and, to a lesser extent, of the liver, showed moderate hyaline-fatty intimal thickening. The changes in the renal parenchyma were not very marked and might be interpreted as a rather slight acute nephritis were it not for the well marked arteriolar changes, the few hyaline glomeruli, the enormous cardiac hypertrophy and the history of hypertension, known to have existed for a considerable time.

CASE 7—R W, a woman, aged 71, admitted, Sept 26, 1923, had had diabetes for years. She had had transitory hemiplegia, a few years before. She had felt well till five weeks before admission, when swelling of the feet, incontinence of urine and mental deterioration set in. She was stuporous when admitted. The blood pressure was 190 systolic, 92 diastolic. Albuminuric retinitis was present. The urine contained sugar, albumin and numerous hyaline and granular casts, but no acetone bodies. Despite the presence of considerable sugar, the specific gravity was only 1020. The blood sugar, on admission, was 465 mg per hundred cubic centimeters, reduced to 165 mg by insulin. The blood chemistry findings were October 1, urea nitrogen, 51.9, uric acid, 5.3, creatinin, 3.1, and sugar, 151, October 3, urea nitrogen, 82.7, and sugar 240 mg per hundred cubic centimeters. The patient died, October 6, after prolonged coma (not diabetic).

Necropsy was performed. The heart weighed 620 gm, all chambers were hypertrophied and dilated, the left ventricle most markedly. The pale, finely granular kidneys together weighed 180 gm. There was marked arteriolosclerosis. There were numerous hyaline glomeruli and atrophic tubules. The majority of the glomeruli were not, however, hyalinized. They exhibited well marked proliferation of the nuclei within the tuft, the capillaries of which were often collapsed or filled with an amorphous, pink staining substance, and were mostly devoid of red cells. Bowman's capsule, in these glomeruli, seemed normal.

These cases illustrate that renal insufficiency may complicate essential hypertension despite the fact that much of the parenchyma has escaped arteriolosclerotic atrophy and obliteration. The glomeruli that have not undergone hyalinization then exhibit proliferative changes which are not present other than minimally in cases with intact renal function. The original opinion of Volhard and Fahr that these changes, which they interpreted as inflammatory, are due to toxic substances of endogenous or exogenous origin injuring a kidney rendered susceptible by already existing arteriolosclerosis, is not supported by adequate evidence and has not met with assent. Neither clinically nor anatomically is there proof that any other pathogenetic factor than the small vessel sclerosis plays a part in the production of the renal lesions in these cases with uremia. It seems very probable that the proliferative changes in the glomeruli are to be regarded as merely a reaction to a rapid course of the arteriolar process, i.e., as analogous to the reaction at the borders of an infarct. I²⁹ have observed similar proliferation of the nuclei of the glomerular tuft as well as leukocytic accumulation in the capillary loops in a case of periarteritis nodosa in which the vasa afferentia were very acutely involved. Weighty evidence that the arteriosclerotic process in these cases has a more rapid tempo than in the cases without uremia is afforded by Fahr's²⁷ statistics, which show that in cases of essential hypertension with associated uremia the patients usually die at a younger age than in those cases not terminated by renal insufficiency. This is borne out by Cases 5 and 6. Were renal insufficiency in essential hypertension usually due to the progression

29 Fishberg, A. M. Zur Kenntnis der Periarteritis Nodosa, Virchows Arch f path Anat 240: 483, 1923.

of the slow obliteration of renal parenchyma till the factor of safety is exceeded, death from uremia should occur at a higher average age than death from cerebral hemorrhage or cardiac failure. But this is not the case.

Clinically and anatomically, the cases of this group may be divided into two stages:

1 A phase of pure hypertension. Though the patients may have no symptoms during this period, which often stretches over many years, its existence is proved at necropsy by the arteriolar changes and the great cardiac hypertrophy, which are obviously not of recent origin.

2 A phase of renal insufficiency, usually of comparatively brief duration. This is apparently coincident with the onset of the glomerular reaction, the histologic characteristics of which indicate its brief duration. The central point of the whole problem—what causes the change from the first, relatively benign, stage to the second period with its fatal renal insufficiency—is totally unexplained. We do not know, aside from the rare cases included under Group 1, why this transition to the stage of kidney insufficiency occurs in so small a proportion of cases of essential hypertension, while the large majority never develop renal symptoms. Whether this change is due to the addition of a functional vasoconstriction to the already present arteriosclerosis,²⁶ or is to be attributed to an acceleration of the arteriolar lesions per se, cannot be said. In contradistinction to nephritis, the reactive changes in the glomeruli are not extensive enough to be regarded as the cause of the uremia. They are merely reactions to, and indicative of, the rapid arteriolar process which, by interfering with the circulation through the kidney, is the actual cause of the renal insufficiency.

3 *Evidence of Cardiac Insufficiency*.—In four cases of the foregoing series, moderate increase in the nonprotein nitrogen of the blood (to over 40 mg urea nitrogen per 100 cubic centimeters) was present. In each of these cases, there was severe cardiac insufficiency, evidenced at postmortem examination by chronic passive congestion of the various organs, including the kidney. In view of the predominant involvement of the renal arterioles by the arteriosclerotic process, it is seen that in essential hypertension the kidney forms a locus minoris resistentiae in the circulation. It therefore suffers from myocardial insufficiency before the other organs, with resultant albuminuria and increase of the nonprotein nitrogen of the blood. In confirmation of this view, I have repeatedly observed that increase in nonprotein nitrogen occurs much more readily in cardiac failure secondary to hypertension than when the circulatory insufficiency follows valvular lesions. The accumulation of nitrogen in the blood thus engendered is usually slight or moderate, not being much above 40 mg of urea nitrogen per hundred cubic centi-

meters in any of the foregoing series I have not seen symptoms of urinary intoxication attributable to cardiac failure alone in the absence of very severe lesions of the kidney or urinary obstruction. Increase of blood nitrogen due to cardiac insufficiency is usually readily differentiated from beginning renal insufficiency by the high specific gravity of the urine, which is "cardiac" in all its characteristics.

RECAPITULATION

1 In seventy-two cases of essential hypertension coming to necropsy, lesions of the terminal arterioles (arteriolosclerosis) were invariably present.

2 In every instance, the minute arterioles of the kidney (*vasa afferentia* and *interlobulares*) were affected.

3 The splenic arterioles were affected in about two thirds of the cases, the pancreatic in about half, the hepatic in less than a third, and the cerebral in about one fifth. The lesions in these organs, when present, were not nearly so marked as in the kidney.

4 The terminal arterioles of the skin, skeletal muscles, myocardium, lungs, gastro-intestinal tract and thyroid were very rarely involved and then to only an insignificant extent.

5 The distribution of arteriolosclerosis is different from that of large vessel atherosclerosis, the latter has its site of predilection in the heart, brain and extremities, while arteriolosclerosis is most frequent in the kidney, spleen and pancreas.

6 The view that hypertension is due to the statically increased resistance offered by organic lesions of the arterioles is untenable. A true generalized arteriolosclerosis does not exist in association with essential hypertension and, therefore, cannot be the cause of the latter.

7 Changes in the arterioles of a nature similar to the arteriosclerosis of essential hypertension occur physiologically with advancing years. Arteriolosclerosis is a pathologic exaggeration of these physiologic changes, resulting from the increased wear and tear incidental to the hypertension.

8 The anatomic changes in the kidney cannot be reconciled with the theory that essential hypertension is due to a disorder of renal function.

9 Only five of seventy-two cases of essential hypertension coming to necropsy had renal insufficiency. Increase in the nonprotein nitrogen of the blood in essential hypertension may occur in three ways, anatomically characterized by:

- a Coalescence of the arteriolosclerotic foci in the kidney.
- b Occurrence of more or less diffuse reaction glomerular changes.
- c Evidence of cardiac insufficiency.

Book Reviews

LECTURES ON PATHOLOGY By LUDWIG ASCHOFF, M.D., Professor of Pathologic Anatomy, University of Freiburg Delivered in the United States, 1924 Thirty-Five Illustrations

This book contains a number of lectures that were delivered by Professor Aschoff, during his recent visit to the United States. It includes, among others, the Lane Lectures of Leland Stanford University, the Janeway Lectures of the Mount Sinai Hospital, New York, and the Osler Memorial and the Harvey Lectures.

Altogether there are fourteen separate papers. The subjects discussed are varied. They cover a wide range of pathologic data and evidently are not intended to form a consistent series. All, however, are concerned with subjects vital to medicine at the present time. Among these subjects, one finds the following: the reticulo-endothelial system, the pathogenesis of human pulmonary consumption, concept of inflammation, pathologic fatty changes, the normal and pathologic morphology of the suprarenals, atherosclerosis, ovulation and menstruation, the orthology and pathology of the extrahepatic passages, the site of formation of bile pigment, thrombosis, the relation of mucosal erosions to the development of ulcers of the stomach, the goiter problem, especially the goiter of puberty, renal secretions, and renal diseases.

It is impossible, in this review, to give a resume or even to state the main conclusions of the author. On all these problems, he has worked and written for years, and these lectures are really condensations of his numerous papers and monographs. For that reason, many physicians will find this book most useful in obtaining fairly concise statements of Aschoff's voluminous writings.

Of greatest interest, probably, are his discussions of the reticulo-endothelial system and the pathogenesis of human pulmonary consumption. More especially, Aschoff discusses, in connection with the reticulo-endothelial system, the morphology and origin of its elements, and then takes up the reaction of these cells in various pathologic processes, laying stress particularly on their relation to blood destruction, to bile pigment production, to their participation in general metabolic functions, such as the metabolism of fat, the metabolism of proteins, and their relation to the storage and metabolism of iron. Of particular interest, too, is his discussion of this system in relation to defense reactions and ferment production.

Aschoff presents concisely his well known views on pulmonary tuberculosis, emphasizing the importance of recognizing a primary infectious stage, characterized by an exudative, rapidly caseating bronchopneumonia, which is usually single. There may be a reinfection, which is usually multiple, this often occurs at the apex of the lung and results commonly in a process of cicatrization and contraction, this forming the productive type of phthisis.

His concept of inflammation is founded on a broad biologic basis. He analyzes in detail the various factors entering into this process, and presents an interesting but exceedingly complex tabular representation of the inflammatory reactions.

Aschoff emphasizes the complexity of the process of thrombosis and discusses several factors in the formation of thrombi. He takes up so-called spontaneous thrombosis, presenting in a masterly way its morphology and the mechanics of its formation. This chapter is recommended especially to the surgeon for his careful consideration.

Attention is called to the interesting chapter on mucosal erosions. Here appear many statements bearing on the origin and prevention of ulcers of the stomach.

To those interested in the study of goiter, his morphologic discussion of the problem will be of interest. He also draws many comparisons between the disease as it appears in Europe and in this country.

The author has a wide range of detailed information not only in the field of morphology, where he stands supreme, but also in biochemistry, bacteriology, immunity, and especially in comparative pathology. From all these sources, he utilizes and correlates important data in the elucidation of disease processes.

THE PHYSIOLOGY OF EXERCISE A TEXTBOOK FOR STUDENTS OF PHYSICAL EDUCATION By JAMES HUFF McCURDY, A.M., M.D., M.P.E., Director of Physical Education Course in the International Young Men's Christian Association College, Springfield, Mass., Editor of the American Physical Education Review Illustrated Pp 242 Philadelphia Lea and Febiger, 1924

This book was written to serve as a guide and text for students and teachers of physical education, and most of the material presented was obtained through studies carried on over a period of more than twenty years at the International Young Men's Christian Association College at Springfield. There is an extensive bibliography, and frequent references to the literature on the subject are made. It deals largely with the effects of exercise and the various forms of athletic contests on individuals, both in regard to general constitutional effects and to the influence of exercise on the various organs, with particular emphasis on functional changes.

Archives of Internal Medicine

VOLUME 35

JUNE, 1925

NUMBER 6

STANDARDIZATION OF THYROID PREPARATIONS *

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Although thyroid is one of the most valuable and specific drugs used in therapeutics, its dosage is largely empiric a given preparation is administered until the desired effect is obtained, but the dosage thus determined does not hold for other preparations and sometimes, as will be shown below, not even for another preparation of the same manufacturer, although it may bear the same label. The doses mentioned in clinical reports are usually meaningless, they seldom convey useful and sometimes convey misleading information. The same is true of the labels on most of the commercial preparations.

This state of affairs, which would be considered intolerable in the case of other important drugs, results from the fact that there is no generally accepted standard for thyroid. There are, moreover, peculiar difficulties in fixing either a chemical or physiologic standard for this drug. Present knowledge of the "active principle" or of principles of thyroid does not aid very materially in the fixing of standards. It is not certainly known in what form the active agent reaches the blood from the gland or from the intestinal tract when the drug is administered by mouth. There is little doubt that the active agent is contained in the iodothyroglobulin of the gland, and the work of Hektoen, Carlson and Schulhof¹ would suggest that this is secreted, to some extent at least, by the gland. There is no evidence, however, that iodothyroglobulin when it reaches the blood is itself physiologically active, I have found that of a foreign species (sheep), when injected intravenously into mice, to be entirely inactive as tested by the delicate acetonitril method (described below). The same preparation given in the same doses by mouth was approximately as active as the entire gland when administered in equiodin doses.² Although the "active principle" is contained in the thyroglobulin, probably as a part of the

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¹ Hektoen, L., Carlson, A. J., and Schulhof, Kamil Precipitin Reaction of Thyroglobulin, Presence of Thyroglobulin in Thyroid Lymph of Goitrous Dogs, J. A. M. A. 81: 86 (July 14) 1923.

² I am indebted to Dr A. T. Cameron for placing the preparations of iodothyroglobulin at my disposal.

molecule, the determination of the amount of this globulin in a gland cannot be used as a method of assay, for the physiologic activity of different specimens of thyroglobulin varies greatly (according to the amount of iodin present). The amount of "thyroxin" (a definite iodin compound which may be obtained from thyroid and which seems undoubtedly to be the essentially active group in the gland) cannot be used as a basis for standardization for, at least with the present methods, there does not seem to be a constant relation between the amount of thyroxin that can be obtained from a gland and the physiologic activity of the latter.

The proposal has been made, but apparently never put into practice, that the gland be standardized by physiologic methods, and a number of these have been suggested. The best of these methods would seem to be the determination of the effects on the basal metabolism in cases of myxedema,³ although probably similar experiments on thyroid-ectomized animals would be satisfactory.

The U S P IX, on the suggestion of Hunt and Seidell, adopted a standard based on the iodin content of the gland, but this standard has been adopted by only a few manufacturers, probably because most clinicians are satisfied to use unstandardized preparations, unsatisfactory results with commercial preparations are usually attributed, without any demonstrated basis in fact, to the age of the preparation, improper methods of manufacture or to some idiosyncrasy on the part of the patient. Moreover, doubts have been expressed recently as to whether the iodin content of the gland is really a measure of its physiologic activity, the belief that thyroid contains physiologically "inactive iodin" in large but variable amounts has been strengthened in some quarters by the fact that only a fraction of the iodin can be secured in combination as thyroxin. It is obviously impossible, however, to draw any safe conclusions as to the physiologic activity of the iodin combination in the thyroid from the products obtained by treating the gland with sodium hydroxid.

I have pointed out, in earlier papers, that there is a close parallelism between the iodin content of different preparations of thyroid and their various physiologic effects. Cameron⁴ has recently summarized the literature on this subject and, with Caumichael, introduced a new method for studying the problem.

INACTIVE IODIN

If however, the iodin content of the thyroid is to be used as the basis for standardization, it is necessary to be certain that glands which are to be used in medicine do not contain "inactive iodin," i. e., inactive

³ Comparisons should be made with Kowitz Ztschr f d ges exper Med 34 457, 1923

⁴ Cameron, A. T. Canad M A J 14 407 (May) 1924

in the sense that some of the iodin is not present in the combination producing the typical effects of thyroid.

Experiments—In investigating this subject experimentally, I have continued to make use of the "acetonitril reaction" (the increased resistance to acetonitril produced in white mice by the administration of thyroid), this seems to be the simplest and most delicate of the tests on animals proposed. The results are, moreover, in entire harmony with the results of other methods and also with clinical experience.

I⁵ have recently discussed certain criticisms that have been made of this method, and emphasized that the test is "specific" only in the sense that an increased metabolic rate is a specific test for hyperthyroidism, in either case, certain other factors must be eliminated. For just as muscular activity, the administration of epinephrin and of certain foods increase the metabolism, so there are factors other than thyroid which will alter the resistance of mice to acetonitril. However, in actual practice there is no more difficulty in determining whether thyroid increases in a specific way the resistance of mice to the nitril than there is in determining whether it is the thyroid which increases the basal metabolism when administered to a patient with myxedema. In the one case, a decigram or two of thyroid is given daily to a patient receiving several hundred grams of food, and in the other a few tenths of a milligram of thyroid are given to a mouse receiving several thousand milligrams of food and the effects of the nitril determined on a group of mice that have received only the food, and on other groups of mice receiving both the food and the minute amounts of thyroid.

In my earliest papers on this subject I did show, however, that certain other glands (testis, ovary, prostate and mammary) when fed to mice increased the resistance to the nitril, but the doses necessary were hundreds or even thousands of times larger than those of the thyroid, there was never the slightest difficulty of distinguishing between thyroid and these other glands. Gellhorn⁶ has recently found that "optones" obtained from some of these glands and also from the thyroid cause a slight increase in the resistance of mice to acetonitril, and concluded that the nitril test is not specific for thyroid. Gellhorn, however, injected from 200 to 300 mg of the optones subcutaneously, and the degree of increased resistance he obtained was far less than that which I constantly obtain when a few tenths of a milligram of the entire thyroid is fed, the effect was also different from that of thyroid, for it continued for several weeks after the injections of the optones were discontinued. So far as I can learn, no evidence has been published to show that these thyroid "optones" have the action most characteristic

5 Hunt, Reid Am J Physiol 63 257 (Jan) 1923

6 Gellhorn Arch f d ges Physiol 200 571, 1923

of thyroid, viz., the increase in basal metabolism especially marked in cases of myxedema (A review of Zondek's "Die Krankheiten der endokrinen Drusen" states that this author found the thyroid optones to have no action on basal metabolism⁷) On the other hand, I found products of the pancreatic and peptic digestion of thyroglobulin to cause a marked increase in resistance to the nitril when fed in doses of from 0.3 to 0.5 mg a day for five days.

I have applied the acetonitril test to about thirty thyroids of adult animals, and have not found a single case in which the degree of resistance produced was not closely proportional to the iodin content, although the latter varied from 0.01 to 0.531 per cent. In some cases, the parallelism was not as close as in others, but I am not certain that the variations were not within the range of the error in the method.

The value of a method of basing dosage on iodin content is best shown, however, by comparing the results of experiments in which this

TABLE 1—Results in Experiment 1*

Preparation	Iodin, per Cent	Weight of Substance Fed per Day (for 5 Days), Mg	Weight of Iodin in Sample per Day Mg	Minimal Fatal Dose of Acetonitril, Mg per Gm of Mouse
Controls	0	0	0	0.45
Thyroglobulin	0.444	0.451	0.002	3.50
Thyroxin	65	0.00462	0.003	2.80
Thyroid 1	0.531	0.376	0.002	3.70
Thyroid 12	0.108	1.851	0.002	3.80
Thyroid 12	0.108	0.376	0.00041	0.42

* In this experiment are included results obtained with a sample of thyroglobulin, and also with thyroxin.

method was used with those in which dosage was based on the amount of the gland (irrespective of the iodin content), in the absence of a standard, the latter method is the one naturally employed.

A typical experiment of this character is given in Table 1, others will be given later.

Thus Thyroids 1 and 12, when fed in equal iodin amounts, had practically the same protective action, the mice being protected against between eight and nine fatal doses of the nitril. When fed in equal doses of substance, Thyroid 1 protected against eight fatal doses, but Thyroid 12 had no protective action.

So far as I can discover, the only experiments reported which suggest that thyroid (that is, thyroid itself, not the products of its hydrolysis) may contain inactive iodin are some that I reported in connection with certain fetal and pathologic glands, a report on two fetal glands

7 Comparison should be made with Loewy and Zondek Ztschr f klin Med 95 282, 1922

by Miura,⁸ and those of Marine and Rogoff⁹ on thyroids recently iodized *in vivo*. The latter authors, experimenting on dogs, state that only a small fraction of the iodin taken up by the thyroid after the injection of potassium iodid had been transformed into active iodin within thirty hours, the tadpole method of assay was used, a method that has been shown not to give trustworthy data as to the activity of thyroid preparations in mammals.¹⁰ I had found that all the iodin that had been taken up by the thyroid of dogs after two doses of iodoform (given by mouth at an interval of twenty-four hours) was in the active form twenty-four hours after the second dose.

I have recently injected sodium iodid intravenously into rats and removed the thyroids at different periods and fed them to mice, and then tested the resistance of the latter to acetonitril. The thyroids removed from eight to sixteen hours after the injection of the iodid had no greater activity than the controls, those removed twenty-four hours after the injection had a marked physiologic action, which was almost, if not quite, as great as that of those removed forty-eight, seventy-two, ninety-six and 144 hours after the injection. The result was the same whether 0.3 mg or 15 mg of sodium iodid per kilogram had been injected, i. e., as I had shown several years ago,¹¹ the amount of iodin rendered "active" did not depend so much on the amount of iodin administered as on the condition of the gland (which could be readily altered by the character of the diet).

The greatest discrepancies that I have found between iodin content and physiologic activity have been in the case of fetal calf thyroids (given me by Dr Frederic Fenger of the Research Laboratory in Organotherapy of Armour and Company). Some of these specimens were marked "normal," others "large," but there was no constant relation between the size of the glands and the amount of iodin and their physiologic activity. Thus a "large" fetal thyroid containing 0.01 per cent iodid was almost as active when fed in equiodin amounts as adult thyroids containing 0.335 and 0.536 per cent iodin, whereas a similar gland containing 0.014 per cent iodin had very slight activity and another with 0.05 per cent iodin was about half as active as a normal adult gland. Of the "normal" fetal glands, one with 0.21 per cent, another with 0.26 per cent and a third with 0.4 per cent iodin had almost the normal activity, whereas one with 0.33 per cent iodin had a very low degree of activity.

8 Miura, M. J. Lab & Clin. Med. 7: 349 (March) 1922.

9 Marine, M., and Rogoff, J. M. J. Pharm. & Exper. Therap. 9: 1 (Oct.) 1916.

10 Swingle, W. W., Helff, O. M., and Zwemer, R. L. Am. J. Physiol. 70: 208 (Sept.) 1924.

11 Hunt, Reid. Experiments on the Relation of the Thyroid to Diet, J. A. M. A. 57: 1032 (Sept. 23) 1911.

Thus, while there are thyroid glands with more or less "inactive" iodin, it is highly improbable that they would be found among those used for medicinal purposes.

Clinical Results—Of course, the final solution of the question whether the standardization of thyroid preparations can be based on their iodin content must come from clinics in which careful observations on basal metabolism are made, evidence from this source is at present very scant, but what there is points very definitely to the conclusion that the iodin standard is valid, or at least that the clinical effects are far more nearly parallel to the iodin contained in the gland than to the absolute amounts of the drug administered.

Magnus-Levy¹² compared the clinical results in different forms of hypothyroidism following the administration of thyroid tablets, iodo-thyrin and a preparation of thyroglobulin containing 1.66 per cent iodin, he administered the preparations, which contained very different percentages of iodin, in at least approximately equiodin doses, and reported that, clinically, the effects of the three were the same. Magnus-Levy also reported that iodothyronin and thyroid (when given in at least approximately equiodin doses) had the same effects on gaseous metabolism. (Other clinicians maintained that iodothyronin was less active than thyroid or thyroglobulin.)

I have recently analyzed and tested physiologically some thyroid preparations used by Dr C. C. Sturgis in the treatment of cases of myxedema. Before treatment, the first patient had a basal metabolism of —38, for three years, his metabolism had been maintained at a level slightly below normal by the administration of thyroid. At the time of these observations, he was receiving daily 0.39 gm of thyroid, which was found by analysis to contain 0.155 per cent iodin, the patient was, therefore, receiving 0.603 mg of iodin in the daily dose of thyroid, and his metabolism was —4. For a period of ten days, the patient took an average daily dose of 0.1947 gm of a preparation of thyroid containing 0.335 per cent of iodin, the iodin, in this dose, was 0.653 mg. The metabolism at the end of ten days was practically unchanged, being —1. Thus, the two preparations had practically the same effect on the metabolism when given in approximately equiodin doses, the absolute amount of thyroid given, however, was twice as great in one instance as in the other. I found, in experiments on mice, that it required approximately twice as much of the iodin-poor as of the iodin-rich thyroid to cause equal degrees of resistance to acetonitrile.

Three months later, the patient, whose metabolism was being maintained at about —6 by an average daily dose of 0.325 gm of thyroid containing 0.155 per cent of iodin, for twenty days took an average

daily dose of 0.117 gm of thyroid with an iodin content of 0.531 per cent. At the end of twenty days, the metabolism had risen to +8, although he had taken little more than a third as much thyroid as in the preceding twenty days. He had, however, received a total of 12.5 mg of iodin in the iodin-rich thyroid and only 10.08 mg of iodin in the iodin-poor thyroid. Animal experiments showed these preparations to have approximately equal activity when fed in equiodin doses, but the one to be almost three times as active as the other when administered in equal doses of the drug itself. Had the iodin-rich preparation been given to the patient in the same doses as the iodin-poor preparation, i.e., if he had received 0.325 gm of the former, there can be little doubt that the results would have been very unpleasant, for even 0.117 gm had had a greater effect on the metabolism than had 0.325 gm of the iodin-poor preparation. Some of the most widely used thyroid preparations contain even higher percentages of iodin than the foregoing, this shows the danger of basing thyroid dosage simply on the amount of drug.

In the foregoing case, an iodin-rich preparation of thyroid had a greater effect on the metabolism than did an iodin-poor preparation, although the dose of the former was little more than a third as great. In the following case, an iodin-poor preparation had a slightly greater effect than one with a higher iodin content when the former was taken in doses containing somewhat more iodin than the latter. The patient, whose metabolism before treatment was —33, had been receiving thyroid for more than three years. At the time of the present observations, the metabolism was —18, and the patient was taking 0.13 gm of thyroid daily, the thyroid had 0.155 per cent iodin, and the patient was therefore receiving 0.202 mg of iodin daily. He received for ten days a thyroid preparation containing 0.108 per cent iodin in daily doses of 0.25 gm, he therefore received 0.27 mg of iodin daily, and the metabolism rose to —11.

Some months later, this patient took a preparation of iodothyroglobulin containing 0.444 per cent of iodin for twenty days, the average daily dose was 0.0704 gm containing 0.312 mg of iodin, and this replaced an average daily dose of thyroid of 0.195 gm, which was supposed to contain 0.155 per cent iodin and therefore 0.307 mg of iodin. In the course of twenty days, the metabolism rose from —16 to —1. In this case, the thyroglobulin appeared to be distinctly more active, in proportion to its iodin content, than the thyroid for it seems improbable that such a small difference in the amount of iodin given could account for the difference in the effect on metabolism, if the iodin was present in the same form in both preparations. I am inclined, however, to think it equally probable that the thyroid tablets varied somewhat in iodin content, as I have found to be the case with other

thyroid tablets, and it may be that a small difference in the strength of thyroid would, in the course of twenty days, have a cumulative action sufficient to account for the difference in the effect on metabolism. Four comparisons of the activity of a sample of these tablets (obtained by grinding up ten tablets) with the thyroglobulin gave practically identical results by the acetonitril test when given to mice in equinodin amounts, for example, in one of these tests, the minimal fatal dose of the nitril after feeding equinodin amounts of the tablets and the thyroglobulin was 3.4 mg per gram of mouse, whereas the controls died from 0.47 mg per gram. The amount of thyroid substance fed daily was 1.251 mg, whereas only 0.451 mg of the thyroglobulin was fed. In another test, however, in which tablets that had not been analyzed were compared with thyroglobulin the latter was distinctly more active when fed to mice in amounts that were supposed to contain equal amounts of iodin, in this case, the minimal fatal dose of the nitril for the mice receiving the thyroglobulin was 2 mg per gram, that for those receiving the tablets was 1.6 mg, whereas the control died from 0.5 mg.

There is not, however, sufficient evidence to maintain that there is an absolute parallelism between the physiologic activity of thyroid and the iodin content, that is, there is not conclusive evidence that all the iodin is in the same form of combination in the normal gland (although there is no evidence for the view that it is not). The important thing is that, with our present knowledge, a far better approximation to correct dosage can be made when this is based on iodin content than when it is based on amounts of gland administered. For example, in the foregoing case a daily dose of 0.0704 gm of thyroglobulin was more effective in increasing the metabolism than was a daily dose of 0.195 gm of the preparation which the patient had been taking, or one part of the former was more than equal to 2.77 parts of the latter. If the iodin-poor preparation had been given in the same dose (i.e., 0.0704 gm) as the iodin-rich preparation, there can be no doubt that the patient would soon have had a relapse. As a matter of fact, the patient had at one time been placed on an average daily dose of 0.087 gm of this preparation and, within a month, his metabolism fell from -4 to -26, that is, 0.087 gm of the iodin-poor preparation was entirely insufficient, whereas 0.0704 gm of the iodin-rich preparation caused a greater effect than was desired. On the other hand, if the iodin-rich preparation had been given in the doses found satisfactory for the iodin-poor preparation, the results would probably have been very unpleasant. As stated above, a daily dose of 0.0704 gm of the iodin-rich preparation had a greater (and undesired) effect on the metabolism than did 0.195 gm of the iodin-poor preparation.

It had been found that 0.195 gm of the iodin-poor preparation was the dose best suited to this patient, if 0.195 gm of the iodin-rich preparation (and there are on the market preparations even more active than this) had been substituted for this, the result would have been that the patient would have received the equivalent of 0.54 gm of the weaker preparation, for, according to the foregoing clinical and also experimental results, 1 part of the stronger preparation was rather more active than 2.77 parts of the weaker preparation. As a matter of fact, less than one half (0.26 gm daily) of the latter had at one time been given to this patient, with the result that the metabolism rapidly rose from 32 per cent below normal to 4 per cent above normal and with a loss of weight of 27 kilograms, and the dose was therefore reduced to 0.195 gm.

I also compared the effects of two of the most widely used thyroid preparations on the resistance of mice to acetonitrile, and found that approximately equal degrees of resistance were obtained when one was fed in doses from five to six times larger than the other. Analysis showed the "stronger" of these preparations to have 5.52 times as much iodin as the weaker preparation. Dr Pelkan of the Children's Hospital found that in the treatment of a case of cretinism (a child 5 months old), these preparations had practically the same therapeutic effect when fed in equiodin doses, the amount of thyroid administered daily in the one case (B) was 9.6 mg, whereas in the other (A) it was 5.3 mg (these statements as to the amount of thyroid in the tablets are based on the assumption that the statements on the labels were correct). These doses (9.6 mg of B and 5.3 mg of A) gave about the optimum therapeutic results, there can be little doubt that, if the doses had been based on the amount of thyroid fed, that is, if 5.3 mg of B or only 9.6 mg of A had been administered, the condition of the patient would soon have altered for the worse. Such a substitution would have been equivalent to increasing fivefold the dose of B, which was giving satisfactory clinical results, or to reducing that of A to one fifth of the dose which experience had shown to be suitable.

COMMERCIAL PREPARATIONS OF THYROID

It is highly desirable that further clinical tests be made with doses of thyroid based on iodin content. Unfortunately, however, the available commercial preparations are not suited for such tests, as is shown by an examination of current drug catalogues. Prof W A Puckner, Secretary of the Council on Pharmacy and Chemistry of the American Medical Association, kindly sent me a summary of the statements concerning thyroid contained in nineteen such circulars. In only five was the assertion made that the preparations were of U.S.P. standard. Reference was made to the iodin content in the circulars of two

other firms it was stated that, in one, the desiccated gland contained not less than 0.3 per cent of iodin in organic combination, in the other that each product represented the stated amount of the fresh gland, containing not less than 0.05 per cent of iodin. Other circulars simply stated that 1 grain of the preparation, or frequently "1 tablet," represents 5 grains of the fresh gland. Physicians at the present time are about as likely to think of thyroid dosage in terms of the fresh gland as they would of the dosage of morphin in the flesh juice of the poppy. Still, the statement that 1 grain of the dried gland corresponds to 5 grains of the flesh gland, or to 5 grains of the fresh gland containing not less than a certain percentage of iodin, may indicate that approximately normal glands are used. But the statement "not less

TABLE 2.—*Analysis of Tablets Obtained from Boston Hospitals or on Open Market*

Tablet Stated to Represent	Iodin per Tablet, Mg	Relative Amounts of Iodin in Tablets	
		Theoretical	Found
1/4 grain fresh thyroid	0.0366	1	1
1/2 grain fresh thyroid	0.0442	2	1.21
1 grain fresh thyroid	0.0992	4	2.71
2 1/2 grains fresh thyroid	0.253	10	6.91
5 grains fresh thyroid	0.439	20	11.98

TABLE 3.—*Analysis of Tablets Obtained in Manitoba*

Tablet Stated to Represent	Iodin Found in Tablet, Mg	Relative Amounts of Iodin in Tablets	
		Theoretical	Found
1/4 grain fresh thyroid	0.0283	1	1
1/2 grain fresh thyroid	0.0363	2	1.28
5 grains fresh thyroid			
a	0.387	20	13.70
b	0.410	20	14.50
c	0.400	20	14.12

than" so much iodin is almost as objectionable from the standpoint of rational and safe therapeutics as would be the statement that a preparation of nux vomica contains "not less than" so much strychnin.

Tablets of the same firm stated to contain equal amounts of thyroid were sometimes found to contain different amounts of iodin and "half-grain" tablets did not always contain twice as much iodin as did "quarter-grain" tablets. Thus, analysis of tablets obtained from Boston hospitals, or bought on the open market, and stated to have been made in the United States, is given in Table 2.

Cameron found similarly labeled tablets obtained from a local pharmacist in Manitoba and stated to have originated in England to contain amounts of iodin as given in Table 3.

When the quarter and half grain tablets were fed to mice in doses containing equal amounts of iodin, the effect on the resistance to acetonitril was practically the same.

When, however, in another series of experiments, the dosage was based on the amount of thyroid stated to be present, that is, when it was assumed that a half grain tablet would have the same physiologic effect as two quarter grain tablets, the quarter grain tablet caused a high degree of resistance in the mice, whereas the half grain tablet had little effect, another indication that thyroid dosage should be based on iodin content rather than on the amount of thyroid. This is of more than theoretical interest if a physician were to substitute one of these half grain tablets for two quarter grain tablets in the treatment of a case of cretinism, for example, the progress of treatment would doubtlessly be interrupted until the proper dosage of the new preparation had been determined.

Physicians in reporting results from thyroid administration usually fail to state whether by a "2 grain thyroid tablet" they refer to a tablet containing 2 grains of dried thyroid or to one containing the equivalent

TABLE 4.—*Results When Quarter and Half Gram Tablets in Doses Containing Equal Amounts of Iodin Were Fed to Mice*

	Iodin in Thyroid Fed Daily for 7 Days	Lowest Fatal Dose of Acetonitril per Gram Mouse
Control	—	0.47
$\frac{1}{4}$ grain	0.002 mg	3.20
$\frac{1}{2}$ grain	0.002 mg	3.50

of 2 grains of the fresh gland, or about one-fifth as much, and, since the percentage of iodin in the thyroid of the tablets that I have examined, assuming that the amount of thyroid present is correctly stated, varies from 0.155 to over 0.7, there is a possibility of one "2 grain tablet" having about twenty-five times the activity of another "2 grain tablet."

Physicians also frequently write of prescribing so many "thyroid tablets" without specifying their source or the amount of thyroid contained in them. There are on the market thyroid tablets containing the equivalent of one one-hundredth grain of the fresh gland, and also tablets containing 5 grains of the dried gland (equivalent to about 25 grains of the fresh gland), or one "tablet" may contain 2,500 times as much thyroid as another "tablet", and since some thyroid has five times as much iodin as other preparations, and the physiologic activity is at least closely parallel to the iodin content, there is the possibility of one "tablet" having the physiologic activity of 12,500 other "tablets".¹³

13 Of course, physicians using exceptionally large or exceptionally small doses of thyroid usually state this fact, but in very many cases, in fact, in most cases, clinical statements as to the dosage of thyroid are practically worthless.

A similar condition obtains in reference to the tablets on the European market a "0.3 gm" tablet may mean 0.3 gm of the fresh gland, "0.1 gm" may mean 0.6 or 0.2 gm of fresh thyroid (iodin percentage usually not stated), "0.4 gm represents an entire fresh thyroid gland of average size," and so on. There are also on the market, both in this country and abroad, a large number of nondescript "thyroid preparations." Some of the various "thyroidproteins" seem to be simply preparations of iodothyroglobulin of various degrees of purity, those that I have tested had a physiologic activity directly proportional to their iodin content. Other preparations are aqueous and other extracts of thyroid are practically free of iodin and have, for all practical purposes, none of the action which makes thyroid such a unique and valuable drug. Such preparations and also the various mixtures of thyroid and other organs have no place in modern, rational therapeutics.

This state of confusion is very unfortunate when attempts are being made to place thyroid therapy on a rational basis, i.e., to bring the dosage into quantitative relations to the metabolism or to other factors.¹⁴

Reference may be made, in this connection, to experiments I have performed in which the amount of thyroid which had been found to cause a well marked increased resistance to the nitril was given in a single dose instead of in divided doses spread over five or six days, mice receiving in a single dose thyroid containing 0.0125 mg of iodin recovered, on the fourth day, from 1.3 mg of acetonitril per gram, whereas those receiving the same amount of thyroid in divided doses in the course of five days did not acquire a tolerance to more than 1 mg per gram, the controls died from 0.24 mg. Thus, it may be possible to base thyroid dosage on the total amount needed, as is the case in some conditions with digitalis.

In other experiments, a physiologic sodium chlorid solution of thyroglobulin (given to me by Dr A T Cameron) was used. One such experiment was as follows. Single doses of 0.2 cc or of 0.4 cc were added to a small amount of the food of a mouse and no other food was given until this was eaten (which was done in the course of a day), the usual food was then continued for four or five days when the resistance of the mice to the nitril was determined. At the same time, similar doses of the thyroglobulin were injected intravenously into mice, they were then continued on the same food as the other mice, and the resistance to the nitril was determined at the same time.

¹⁴ Comparison should be made with Boothby, in Oxford Medicine **3** 950, 1922, Kowitz (Footnote 3), Nobel E, and Rosenbluth, A Wien klin Wchnschr **37** 641 (June 26) 1924.

In another experiment, with a different preparation of thyroglobulin, the mice injected with the thyroglobulin were distinctly less resistant than the controls thus, the latter died from 12 mg of nitil per gram, those injected with 0.3 and 0.4 cc of the globulin died from 0.8 and 0.9 mg of the nitil, whereas it required 1.7 mg per gram to kill the mice given these doses by mouth at a single feeding.

Detection of Adulterated Thyroid—Muscle tissue treated with a solution of potassium iodid and dried and powdered is alleged to have been sold as thyroid, many proprietary “anti-fat remedies” contain thyroid, whereas others contain potassium iodid, extract of bladderwrack and other iodin compounds. Hence, it is desirable to have tests by which nonthyroid as well as thyroid-iodin may be detected. In the case of the inorganic iodids and many of the organic iodin compounds, simple chemical tests suffice. A test of this kind was included in U S P VIII, it consisted in treating a cold aqueous extract of the preparation

TABLE 5—*Results in Experiment 21*

	Minimal Fatal Dose of Acetonitril Mg per Gram Mouse
Controls, normal food	0.55
Mice injected with 0.2 and 0.4 cc of thyroglobulin solution	0.55
Mice fed a single dose of 0.2 cc of thyroglobulin solution	1.4
Mice fed a single dose of 0.4 cc of thyroglobulin solution	2.3

with sodium nitrite, acidifying with concentrated nitric acid and shaking with chloroform. A more delicate test consists in mixing the suspected material with a drop of starch paste on a white tile, a number of the so-called iodin-protein compounds caused a blue color at once, showing the presence of free iodin, and a large number of “organic” iodin compounds and a number of “anti-fat remedies” developed a blue color on the addition of a drop of concentrated nitric acid. Some of these iodin compounds could readily be detected, in this manner, when mixed with thyroid in the preparation of 1 part to 750 parts of thyroid. Other chemical tests can be employed to distinguish between many organic iodin compounds and thyroid, but it is probable that, in some cases, the detection of foreign iodin compounds in mixtures containing thyroid would offer considerable difficulty and might be impossible at present when very small amounts of material are available. By the acetonitril method, however, it is possible to determine with a considerable degree of accuracy how much of the iodin contained in a complex mixture of iodin containing compounds is present in thyroid, this can readily be done when only a few milligrams of material are available. The principles underlying this method were discussed in

detail, several years ago, by Seidell and myself¹⁵. Briefly, they are as follows. No iodin compound was found which, in any dose, caused an increase in the resistance of mice at all comparable to that caused by thyroid, thus, in a large number of experiments in which a few milligrams of thyroid were fed to mice, the average degree of protection against the nitril was 137, that is, the mice recovered from 137 times the dose of the nitril fatal to the controls. No nonthyroid iodin compound was found which caused, except very rarely, an increased resistance of more than 2, even when the preparation was fed in amounts containing hundreds or thousands of times as much iodin as the thyroid. We suggested that the nonthyroid iodin compounds caused an increased resistance only through their iodin being available for increasing the active principle in the mouse's own thyroid, we showed that the extent to which this occurred was determined by the condition of the mouse's own thyroid, and that this could be modified by changes in the diet.

There were, however, differences between iodin compounds in their action in increasing the resistance of mice to the nitril and also in increasing the activity of the thyroids of rats to which they had been administered. Thus, some extracts of bladderwrack had a slight protecting action when fed to mice in amounts containing only from fifteen to thirty times as much iodin as in the minimum amount of thyroid which was detectable by the test, with no dose of bladderwrack, however, was it possible to more than double the resistance of the mice. It was necessary, in these experiments, to give very many times as much iodin in the form of potassium iodid to secure any detectable effect, thus, the iodin in bladderwrack seemed to be more available as a source of iodin for the thyroid than was that of potassium iodid. (Such iodin compounds were called "thyreotropic".) Some iodin compounds seem unable to serve as a source of iodin for the thyroid, tetraiodophenolphthalein,¹⁶ for example, when fed to mice had no effect on their resistance to the nitril nor, when injected intravenously into rats, did it increase the activity of the thyroids of these animals (as was the case when sodium iodid was injected).

When the foregoing principles were applied to mixtures of thyroid and other iodin compounds, there was no difficulty in detecting a few thousandths of a milligram of nonthyroid iodin or a few thousandths of a milligram of thyroid-iodin, although this was mixed with thousands of times as much nonthyroid iodin. In Table 6 are given typical experiments of this character.

15 Hunt, Reid, and Seidell, A. J. Pharm & Exper Therap 2: 15, 1910.

16 This compound was studied because it has been found to be a constituent of a widely advertised "anti-fat remedy" (J. A. M. A. 82: 734 [March 1] 1924), it was thought that it might have some especial relation to the thyroid as has the iodin compound of some extracts of bladderwrack.

We may suppose that, in Series 1 of Table 6, *b* had been prepared from thyroid known not to be adulterated with any foreign iodin compound and that *c* (an unknown) had been found by analysis to contain 0.218 per cent of iodin, when fed in daily doses containing 0.00218 mg of iodin, it had slightly less activity than 0.0011 mg of iodin in *b*, and we would conclude that not more than half the iodin was in thyroid combination, about a fourth the iodin in *d*, none of that in *e* (although it had nearly 4,000 times as much iodin as *b*) and all that in *f* would be considered to be in thyroid combination.

In Series 4, there would be some doubt as to whether all the iodin in *e* was present in thyroid because the protection afforded by thyroid was probably near a maximum with a smaller amount of iodin, this question could be answered by repeating the experiment, feeding only as much iodin of the unknown *e* as was contained in *b*, when the degree of protection should be practically the same.

TABLE 6—*Results in Additional Experiments*

Series	Drug or Mixture Fed	Mg Iodin Fed Daily as		Total Mg Iodin in Drug or Mixture Fed	Fatal Dose of Acetonitril in Mg per Gm	Ratio of Increased Protection
		Thyroid	Other Compound			
1 a	Controls	0	0	0	0.18	1.0
b	Thyroid alone	0.0011	0	0.0011	0.95	5.3
c	Thyroid plus potassium iodid	0.0011	0.00108	0.00218	0.77	4.3
d	Thyroid plus potassium iodid	0.0011	0.0029	0.004	0.98	5.4
e	Potassium iodid alone	0	3.82	3.82	0.20	11
f	Thyroid alone	0.002	0.0	0.002	1.8	10.0
4 a	Controls	0	0	0	0.54	1.0
b	Thyroid alone	0.00053	0	0.00053	2.0	3.7
c	Thyroid plus potassium iodid	0.00053	0.1986	0.19913	2.2	4.1
d	Potassium iodid alone	0	0.1986	0.1986	0.56	1+
e	Thyroid alone	0.0015	0	0.0015	4.0	7.4

Many similar experiments were performed in which iodin compounds other than potassium iodid were used, the results were the same. Dr Seidell also prepared a number of mixtures similar to the above and, without knowing their composition, I was able to determine the approximate amount of thyroid-iodin contained in them, many experiments involving the use of a large number of mice were, however, necessary.

It is of interest to note in connection with the recent use of iodin¹⁷ in the treatment of exophthalmic goiter that in these experiments we did not find nonthyroid iodin to have a distinct or constant antagonistic action to the thyroid, usually, the foreign iodin compound, when fed in relatively large doses, slightly increased the protection afforded by the thyroid.

¹⁷ Loewy, A., and Zondek, H. (Deutsch med Wchnschr **47** 1387 [March 31] 1921) used potassium iodid. Plummer and others in this country use a preparation containing free iodin.

These results are somewhat analogous to those recently reported by Starr, Segall and Means,¹⁸ who found that the administration of iodin did not reduce the thyrotoxicosis from the ingestion of thyroid and those of Sturgis (quoted by these writers) who found, in experiments on rabbits, that previous iodinization had no influence on the toxic effects of thyroxin.

I also found that the activity of rats' thyroids (determined by removing and feeding them to mice) was not altered by the intravenous injection, six hours before the rats were killed, of large doses of sodium iodid; this was also true when the activity of the rat thyroids had been increased about twofold by the intravenous injection, forty-eight hours previously, of small doses of sodium iodid. On the other hand, I did find, in some experiments planned to test the suggestion made by Oswald that iodin increases the secretion of the thyroid gland, as well as makes the secretion more active, that the intravenous injection of sodium iodid into mice lowered their resistance to acetonitril for a day or two, results which suggest that possibly the iodids have an inhibitory effect on thyroid secretion. The latter suggestion has been made, and rejected, by Hildebrandt,¹⁹ who found that "small" doses of potassium iodid lowered the metabolism not only of normal but also of thyroidectomized rats. The doses used by Hildebrandt for rats were, in proportion to body weight, from six to 300 times as large as those which I used for mice.

SUMMARY

The physiologic activity of thyroid preparations as determined by the acetonitril test on mice and by clinical observations was found to be closely parallel to the iodin content.

Little or no physiologically inactive iodin was found by these tests in the thyroids of adult animals.

Very small amounts of nonthyroid iodin in adulterated thyroid preparations could be detected by the acetonitril test and also by simple chemical tests.

Very few of the thyroid preparations on the market comply with the U. S. P. standard, they were found to vary greatly in physiologic and therapeutic activity.

¹⁸ Starr, Paul, Segall, H. N., and Means, J. H. The Effect of Iodin in Exophthalmic Goiter, *Arch. Int. Med.* **34**, 355 (Sept.) 1924.

¹⁹ Hildebrandt Arch f. exper. Path u. Pharmakol. **96**, 292, 1923.

NAUSEA AND RELATED SENSATIONS ELICITED BY DUODENAL STIMULATION

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The purpose of this paper is to present the results of a clinical and laboratory study of sensation arising from stimulation of the duodenum. The chief of these sensations is nausea. Since nausea is a sensation, its presence must be identified with some objective or motor phenomenon before it can be studied by animal experimentation. Up to the present, no adequate studies dealing with the mechanism of nausea have been noted in the literature. I therefore believe that the present experiments open up a field for investigation, and hope that the data presented may stimulate further work on this important subject.

METHODS

The present study was made on a series of sixty ambulatory patients, the majority of whom complained of gastro-intestinal disturbances. In the number were many women, and prominent among their complaints were symptoms suggestive of circulatory instability. The Rehfuss tube was used for duodenal drainage. The stomach was usually washed with warm water, and then the bulb was allowed to pass into the duodenum. Four test solutions were injected serially: 30 per cent magnesium, 15 per cent disodium phosphate, 2 per cent hydrochloric acid, and 2 per cent sodium bicarbonate. In considering the method of drainage employed, it is evident that we are dealing, on the one hand, with certain mechanical stimuli, such as the presence of the bulb in the duodenum and the distention of the intestine with the injected fluids, and, on the other, with chemical stimuli. It soon became evident that 2 per cent hydrochloric acid and 2 per cent sodium bicarbonate had no effects demonstrably different from the other solutions, so the use of these was discontinued.

EXPERIMENTAL RESULTS

The Production of Nausea.—The data which have been collected will be used to illustrate the points under discussion, since they do not lend themselves readily to statistical presentation. Some fifteen to twenty minutes were usually consumed in swallowing the tube and washing the stomach. It was customary, at this point, to have the patient continue swallowing the tube until the duodenal mark was reached. During these swallowing movements and after they were completed, a conversation was kept up in order to prevent, as far as possible, the development of psychic inhibitory impulses to stomach and pylorus. It was no uncommon experience to have such a conversation interrupted without warning.

by a transitory wave of nausea. This would be followed by a flow of bile stained material from the tube. Sometimes a change of position from the supine to the erect or from the right side to the prone precipitated such an attack. Indeed the appearance of a transitory attack of nausea came to be regularly regarded as a signal that the bulb had passed into the duodenum, and that now the test solutions might be injected.

In Case 19, the bile was flowing freely. Magnesium sulphate was injected and was followed by a wave of nausea. The reaction of the material draining from the tube became strongly acid. This experience recurred three times before a satisfactory sample of bile was obtained. As a working hypothesis, it was assumed that, with each wave of nausea, the bulb of the tube had been returned to the stomach. In Cases 225 and 255, this interpretation was checked by means of a fluoroscopic examination. A satisfactory sample of bile was obtained in each case, and then an injection of magnesium sulphate in one case, and sodium phosphate in the other, was made. Immediately, a wave of nausea resulted, and the reaction of the material draining from the tube became strongly acid. The fluoroscope now showed that the bulb was lying in the stomach. The most striking example of nausea was found in Case 6. The patient had been a sufferer from headaches, dysmenorrhea and indefinite gastro-intestinal symptoms for a long time. The gallbladder and appendix had been removed six months previously. More recently, she had complained of daily attacks of dizziness. After swallowing the bulb, the patient was quite comfortable for a period, then nausea of a low grade, accompanied by dizziness, manifested itself. Magnesium sulphate was injected, drop by drop, and a typical flow of bile resulted. On the completion of this collection and while the nausea still persisted, the tube was withdrawn to the stomach mark. Nausea ceased at once, but the dizziness persisted for a period. There can therefore be no doubt that nausea results from the use of the tube in the manner described. It is next important to determine the origin of the stimulus producing the sensation.

Does the Sensation Arise from the Pharynx?—It is a well established fact that stimulation of the pharynx readily leads in many subjects to vomiting. Indeed, it is difficult for the patient to swallow the bulb on the first trial because of this factor. However, when the bulb is once in the esophagus, the tendency to vomit lessens. Only occasionally is a patient found whose pharynx is so sensitive as to resent the presence of the tube, once it is in place. If these patients are asked relative to the sensation which arises from the presence of the tube, they speak of it as "gagging" and state that there is a feeling that they are going to vomit. They do not characterize it as nausea. Any observer may readily verify these statements on himself, as I have done. The injection, through the

tube, of water of distinctly different temperature from that of the body may elicit unpleasant sensations to which no immediate description is applicable, but these sensations are not nausea. In fact, it is hard to see how a constant stimulus, such as the presence of a tube in the pharynx, would be interpreted at unexpected moments as a sensation of nausea.

Does the Sensation Arise from the Stomach?—The stomachs of all the patients were washed as a matter of routine. At times the washing was vigorous. Water of varying temperatures was used. During this process nausea was elicited in no instance. In fact, it is a matter of clinical experience that in the presence of persistent nausea, gastric lavage does not increase nausea but rather relieves it. I¹ have washed the stomachs of a large number of dogs and rabbits through gastrostomy openings. If the stomach of the dog was distended unduly, he wouldgulp once or twice and empty it through the mouth. There was no salivation or licking of the nose which would indicate the presence of nausea.

Does the Sensation Arise from the Duodenum?—A consideration of the evidence presented, in the cases cited and others of the same series, leaves no doubt as to the location of the bulb in the duodenum at the time nausea appeared. It was decided, however, to check this point on a dog with a gastrostomy. The bulb was introduced, under ether anesthesia, into the duodenum, and the rubber tube was brought to the abdominal surface through the gastrostomy wound. The next day, the stomach was washed thoroughly, even roughly, with a second tube introduced into the gastrostomy. Into the latter tube, also, the test solutions were injected. Finally, with the palpating finger, the duodenal tube was traced to the pylorus. From none of these manipulations did salivation or licking of the nose (evidence of nausea) result. At this point, 5 c.c. of 15 per cent disodium phosphate was injected rather rapidly into the duodenal tube. The animal began to salivate, licked his nose, and gave a few retching movements, but he did not vomit. I think it is safe to say that, in this case, we have an experiment which duplicates the clinical ones cited above. On another occasion, an attempt was made in the same animal to introduce beyond the pylorus a Rehfuss tube and a tube carrying a rubber balloon, so that tracings of the movements of the duodenum could be registered. As soon as the animal waked from the anesthetic, an antiperistaltic wave returned both tubes to the stomach. This occurred despite the fact that the balloon and bulb were placed well beyond the pylorus, presumably close to the jejunum. This irritability of the duodenum has been noted by other workers. Thus,

¹ Keeton, R. W., and Koch, F. C. Am J Physiol **37** 481, 1915. Luckhardt, A. B., Keeton, R. W., Koch, F. C., and La Mer, Victor. Am J Physiol **50** 527 (Jan.) 1920. Keeton, R. W., Koch, F. C., and Luckhardt, A. B. Am J Physiol **51** 454, 469 (April) 1920.

Luckhardt, Phillips and Carlson,² in their studies on the pylorus, observed that reflex emesis is certainly more readily elicited from mechanical irritation of the duodenal mucous membrane near the pylorus than from simple irritation of the gastric mucosa.

The ease with which nausea is elicited appears to be a rough index of duodenal irritability. Subjects having the greatest irritability show nausea when the bulb of the tube is either present in the duodenum or moved slightly. Others, having less irritability, respond with nausea when the fluid is injected sufficiently rapidly to cause a distention of the intestine. Still others have nausea only after a definite latent period has elapsed subsequent to the injection of magnesium sulphate or disodium phosphate. Of these two, the disodium phosphate is more potent in producing the symptoms, but it has less effect in establishing a flow of bile. The presumption therefore is strong that, in searching for the origin of nausea, attention will be fixed primarily on the movements of the duodenum rather than on a mechanism which is effective in causing the discharge of bile. Thirty-four of the cases examined showed no nausea or other symptoms. Even in the same patient, there were variations from day to day in the ease with which symptoms were elicited.

Other Symptoms Elicited by Duodenal Stimulation.—Dizziness was the next most definitely described symptom that resulted from the use of the tube. Five of the twenty-six cases that showed symptoms complained of it. One patient (Case 6) described the dizziness as coming in waves, another (Case 19) spoke of it as "light headedness." In two of the cases (Cases 124 and 204), nausea also was present with the dizziness. In the others, dizziness appeared without the nausea. In Case 6, the dizziness persisted until the tube was completely removed from the mouth while the nausea disappeared when the bulb was drawn back into the stomach. The same patient had intermittent attacks of dizziness during the remainder of the day. In the other cases, the dizziness was quite transitory.

Pressure Sensations Referable to the Head.—There was a third group of sensations which have been variously described by the patients, but which, for convenience may be grouped under the term of "pressure sensations." This term, pressure, is involved in all the descriptions given by the patients, and in using it there was no intention of conveying the idea that there was an actual increased intracranial pressure, although such may exist. The patient was asked to describe, as accurately as possible the sensations produced. His phraseology has been included in the accompanying table. Since the opportunity of studying these cases was often limited, the diagnoses are provisional rather than final.

² Luckhardt, A. B., Phillips, H. T., and Carlson, A. J. Am. J. Physiol. 50: 57 (Oct.) 1919.

Headache—In five cases (Cases 124, 156, 167, 214 and 204), the head discomfort became so sharp that the patients characterized it as true headache. Three of these patients were sufferers from migraine. In Case 167 the headache which followed the stimulation was in the same location (left eye and left occipital region) in which the migraine headaches were customarily located. In the other two (Cases 156 and 214), the location and duration of headache were different. The fourth patient (Case 204), who had been previously under treatment for duodenal ulcer, found that the duodenal drainage on one occasion gave her relief from a persistent headache. The fifth patient (Case 124) found

Pressure Sensations Referable to Head

Patient	Sensation	Manipulation	Diagnosis of Case
19	Bigness of head	During injection of magnesium sulphate	Undetermined (cholecystitis?), postoperative adhesion
28	Fulness of head	Aspiration of duodenal contents with syringe	Hyperthyroidism, cholecystitis?
49	Pressure over top of head, tightening of band about forehead	After injection of magnesium sulphate during the resulting flow of bile	Migraine
97	Fulness over forehead and eyebrows	Distention of duodenum following gravity injection of magnesium sulphate, relieved by discontinuing injection	Hypertension, cholelithiasis proved by operation
126	Tightness between the eyes	After magnesium sulphate and disodium phosphate injections	Infected teeth, infected tonsils, menopause
160	Heavy feeling in head and over eyebrows	After magnesium sulphate injection	Undetermined, chronic appendix suspected
162	Fulness between eyes, extending to temples	Present during injection of magnesium sulphate, relieved on discontinuing injection	Colitis, etiology undetermined
172	Fulness of head	Following injection of magnesium sulphate and sodium phosphate	Cholecystitis (not operated on)
255	Heaviness about the eyes	Ten minutes after magnesium sulphate injection and during flow of bile	Chronic appendicitis, menopause, migraine

that a slight headache, which was present at the onset of duodenal manipulation became much worse before the drainage was terminated. In studying the rôle of the intestines in hunger with a balloon in the duodenum and one in the stomach, Ivy recently observed that when the hunger period begins nausea and headache occur, and that vigorous hunger contractions do not occur because of inhibition. The distention of the duodenum by the balloon might, in this case, be regarded as the effective stimulus in causing the nausea and headache.

Neck Sensations—In six of the cases (Cases 41, 96, 167, 175, 222 and 248), there were sensations referable to the neck. These were

³ Ivy, A. C. Personal communication to the author. Data to be published soon.

described as "tightening of neck muscles, drawing of the neck, stiffness of the neck, pressure over the neck and aching of the neck." In more than one instance, it was stated that the sensation aroused a desire to massage and rub the neck.

Syncope—In Case 115, a rather remarkably organized syndrome resulted from the injection of the magnesium sulphate. Shortly after the injection, the patient developed pain in the back of the head which radiated anteriorly across the eyes. This was followed by a sense of weakness, faintness and three attacks of syncope. On recovering, she stated that there was a "wooden feeling" in both legs. This patient had developed a similar spontaneous attack ten days before this experimentally produced one. This spontaneous attack was afterward followed by tenderness over an incision through which the gallbladder had been drained, and by pain beneath the right shoulder blade.

These experimental data, therefore, seem to show that the definite sensations enumerated above result from the stimulation of the duodenum. It will be noted that one of these (nausea) has a definite entity. It was quite constantly present whenever the duodenum was at all irritable. The others were less constantly present, were less definitely described by the patients, were often merged into each other, and might be accounted for on a circulatory (vasomotor) basis. Later, the question of the relation of this circulatory group of sensations to nausea will be considered more fully.

COMMENT

Stimulation of the Duodenum—It is important to know what results have been reported by other observers from duodenal stimulation.

On the motor side, it was observed by Wheelon and Thomas⁴ that in anesthetized animals elevations in duodenal tonicity are associated with reductions in the height of antral waves. McClure, Reynolds and Schwartz⁵ studied, under the fluoroscope, the behavior of the stomach in five men who had previously swallowed a duodenal tube. When the duodenal bulb was moved, the gastric peristalsis in two cases became shallow, in another, ceased for several minutes, and in a fourth changed into a pylorus spasm. Brunemeier and Carlson⁶ have shown that stimulation of the duodenum inhibits the tonus and contractions of the empty stomach. These observations demonstrate the existence of a state that is necessary for antiperistalsis. The presence of antiperistalsis following duodenal stimulation has been previously reported in man by

4 Wheelon, H., and Thomas, E. J. Am. J. Physiol. **59** 72 (Feb.) 1922.

5 McClure, C. W., Reynolds, L., and Schwartz, C. O. On the Behavior of the Pyloric Sphincter in Normal Man, Arch. Int. Med. **26** 410 (Oct.) 1920.

6 Brunemeier, E. H., and Carlson, A. J. Am. J. Physiol. **36** 191, 1915.

Ivy⁷ and by Lehman and Gibson,⁸ and in the dog by Ivy and McIlvain.⁹ Two other motor phenomena also have been described a maintained contracture or tonus of the duodenum, by Wheelon and Thomas,¹⁰ and an increase in the tone of the pylorus, by Carlson and Litt.¹¹

On the sensory side, Ivy⁷ noted that the injection of an alkaline solution in man gives rise to marked nausea followed in two instances by abdominal vomiting. Lehman and Gibson⁸ also report nausea following the introduction of a catheter through a jejunal fistula into the duodenum. McClure, Reynolds and Schwartz⁵ noted that nausea followed the withdrawal of the Rehfuss bulb into the third part of the duodenum in one of their subjects.

If nausea is to be related to a duodenal motor phenomenon, it may then originate from any one of these three activities antiperistalsis, increased tonus of the pylorus, or increased tonus of the duodenum. Boas,¹² from purely clinical observations, considered that nausea was associated with abnormal peristalsis. Alvarez¹³ believes that nausea may be one of the symptoms elicited by an intestinal antiperistalsis. He states that the vivid description, by patients, of nausea as coming in ascending waves suggests that they may be actually feeling reverse waves in the bowel. It is a common observation among roentgenologists that a sudden cessation of the antral waves with a relaxation of the fundus almost always indicates that the patient is nauseated. As previously emphasized, this relaxation is a necessary condition for antiperistalsis. Hesse¹⁴ states that, at the beginning of nausea, there exist recognizable peristaltic waves in the antrum which are followed immediately by a contraction of the pylorus "in toto" and a relaxation of the fundus. This description would easily lend itself to a duodenal origin of the stimulus. Hatcher and Weiss¹⁵ give experimental data showing that cats nauseated with tincture of digitalis resist strychnin poisoning much better than normal animals, which would be explained by a delay in the absorption of the strychnin. They further state that, when a nauseant is absorbed, the pylorus closes and remains closed during the continuance of nausea.

7 Ivy, A C Am J Physiol **46** 340 (July) 1918

8 Lehman, E P, and Gibson, H V Jejunal Fistula, J A M A **82** 1918 (June 14) 1924

9 Ivy, A C, and McIlvain, G B Am J Physiol **67** 124 (Dec) 1923

10 Wheelon, H, and Thomas, E J J Lab & Clin Med **7** 375 (April) 1922

11 Carlson, A J, and Litt, S Visceral Nervous System, Reflex Control of Pylorus, Arch Int Med **33** 281 (March) 1924

12 Boas Berl klin Wochenschr **46** 1101, 1909

13 Alvarez, W C Reverse Peristalsis, J A M A **69** 2018 (Dec 15) 1917

14 Hesse, O Arch f d ges Physiol **152** 1, 1913

15 Hatcher, R A, and Weiss, Soma J Pharmacol & Exper Therap **22** 139 (Oct) 1923, Seat of Emetic Action of Digitalis Bodies, Arch Int Med **29** 690 (May) 1922

For this statement they furnish no evidence, unless it is drawn from the work of Hesse.¹⁴ Patients suffering from dizziness always described the sensation as of a wavelike character. Not infrequently but not so constantly, the same description is applied to nausea. It is therefore obviously impossible in the present state of knowledge to connect nausea with any particular motor phenomenon of the duodenum. This must be reserved for more accurate physiologic studies. A pathologic duodenal antiperistalsis would, however, explain the production of this symptom very satisfactorily from a clinical point of view.

Is All Nausea of Duodenal Origin?—Nausea may originate from widely different afferent fields—the bladder when distended, the pregnant uterus, the pelvis and the ureters of the kidney, the colon, the appendix, the heart, the brain under pressure, and any peripheral nerve when traumatized. Alvarez,¹⁶ who regards nausea as a symptom of antiperistalsis, believes that the aboral passage of food is dependent on a metabolic gradient in the intestines. The point of high metabolism is in the jejunum, and of low metabolism in the colon. If these relations are reversed by nervous or humeral agents, there is a reversal in peristalsis and a regurgitation of chyme occurs. If a pregnant uterus can cause a contraction of the pylorus and emesis, it can as readily cause motor phenomena in the duodenum, which could be recognized as nausea. It is, of course, established that eviscerated animals¹⁷ can be made to vomit. They also may show some of the other reflexes associated with nausea (salivation), but this does not mean that the animals have the sensation of nausea. In other words, there is nothing in the literature that makes the foregoing conception untenable. It simply must be investigated experimentally.

THE VOMITING ACT

For an understanding of nausea and these related sensations, one must review the mechanism of vomiting. Clinically, the vomiting act is divisible into two phases, a prodromal and an emesis phase. This prodromal period manifests itself by the presence of many sensations which are difficult to describe. Chief among these is nausea. The patient may recognize waves of dizziness, or he may complain of fulness and pressure in the head. If he has a sick headache, the head pain will be present, and in some cases this, too, is relieved with the onset of emesis. It is difficult to secure sufficient cooperation from a patient to obtain an adequate description of his symptoms. He usually summarizes the

16 Alvarez, W C Am J Physiol **37** 267, 1915, The Motor Functions of the Intestine from a New Point of View, J A M A **65** 388 (July 31) 1915
Alvarez, W C and Starkweather, E Am J Physiol **46** 186 (June) 1918
Alvarez, W C Physiological Rev **4** 352 (July) 1924

17 Eggleston, C, and Hatcher, R H J Pharmacol & Exper Therap **3** 551, 1912

situation by saying, "I am sick." On the motor side, it will be noted that he is extremely pale, that his hands, forehead and neck are sweating, that the arrectores pilorum muscles are contracted with the production of the so-called "goose flesh," and that salivation is profuse. With the onset of swallowing movements, the second stage, the stage of emesis, appears. This stage has been described as a convulsive process involving the respiratory mechanism, the muscles of the esophagus and stomach, the abdomen and the body in general. This stage of emesis is predominantly a motor phase. All the sensations present prior to its onset are at once relieved. The patient is no longer weak, sick and nauseated. He is well and remains so until the cycle swings again to the prodromal phase. There may be many combinations of these two phases, and emphasis may be placed on one or the other. The prodromal phase may exist for a long period without development of emesis, or it may be so transitory as to escape notice. Such patients are then said to suffer from vomiting without nausea. Thus, in the case of rats,¹⁵ emesis does not occur. It should be appreciated that each phase has its own pattern of reflex integration. The prodromal phase develops an evidently sensory pattern and the emesis phase, a motor one.

All the facts relative to the stage of emesis have recently been completely discussed by Hatcher.¹⁶ With this phase of the vomiting act, the present discussion is not concerned. It is this prodromal stage, which is so easily recognized clinically, that requires a physiologic analysis. The physiologists have always started their discussions of vomiting with the movements of the stomach, as evidenced by Hatcher's recent review.¹⁸ Clinicians, on the other hand, have been repeatedly furnishing evidence that in vomiting regurgitation of intestinal contents is an important feature of the act. Thus, Ewald¹⁹ has reported that in ileus the stomach is filled with intestinal contents long before fecal vomiting occurs. All this evidence has been quite completely reviewed and summarized by Alvarez.¹⁶ The motor phenomena of this phase would then consist of the establishment of intestinal antiperistalsis with a consequent regurgitation of chyme into the stomach. Logically, then, this stage might be spoken of as the "stage of regurgitation." It would be in sharp contrast to the "stage of emesis," in which the motor activity involves the gastric, esophageal, respiratory and skeletal muscles.

Some of the vomiting afferent impulses, originating in the heart and in the duodenum, have been shown by Hatcher and Weiss¹⁵ to be mediated through the sympathetics. It would be expected that the reflex spread would be through connections most intimately associated with the sympathetic system. So the vasomotor center and vasomotor nerves

¹⁸ Hatcher, R. A. *Physiological Rev.* **4** 479 (July) 1924

¹⁹ Ewald, C. A. *Berl. klin. Wchnschr.* **44** 1416, 1907

would be involved. The resulting vascular activity doubtless explains the dizziness, weakness, pressure sensations in the neck and head, the headache and the syncope, which may be observed clinically in vomiting, and which have been produced experimentally by duodenal stimulation. The reflex spread would involve further the secretory mechanism, with resulting salivation and sweating and, later, the muscles of the hairs, with a production of "goose flesh." At this point, it should be realized that almost every writer who has discussed nausea in an experimental animal, and who has written in his protocols the words, "Nausea exists," has reached these conclusions because he has observed the animal salivating, because he has seen a look of dejection about the animal, and because he has realized that when these phenomena are present in man, *man then experiences the sensation of nausea.* This sensory prodromal stage develops all its sensations from reflexes spreading through the vegetative (sympathetic autonomic) nervous system, and for this reason they are described with difficulty. When the storm sweeps into the stomach, esophagus and skeletal musculature, then the sensations formerly present cease, and the "stage of emesis" is initiated. Hatcher and Weiss¹⁵ have presented a teleologic view of nausea in which it was shown to be highly advantageous to a rat to delay his food in the stomach, thus rendering the absorption quite slow. With a slow absorption time, opportunity would be given for oxidation of the ingested poisons, and the rat would not secure, at any given moment, a lethal dose of toxins. The loss of vomiting then becomes an adaptation of the animal to the character of his food and the exigencies under which he secures food. While this is interesting, it in no way involves a physiologic analysis of the mechanism of nausea.

SUMMARY

1 A study was made of the sensations arising from duodenal stimulation in a group of patients, of whom many showed symptoms of circulatory instability. Chief among these sensations was nausea. Dizziness, pressure sensations referable to the head and neck, headache and syncope also were elicited.

2 When the mechanism of the production of these sensations was considered, it was suggested that nausea resulted from a motor duodenal dysfunction, most probably from a pathologic antiperistalsis. The other sensations were regarded as of circulatory origin, and were explained on the basis of a reflex spread into the vegetative (sympathetic-autonomic) nervous system, involving primarily the vasomotor mechanism.

3 The vomiting act was considered as divisible into two stages: to the first, or prodromal stage, the name of "regurgitation" might be appropriately given, since the primary motor phenomenon of this stage consists of an intestinal antiperistalsis. Secondary motor phenomena

are to be found in salivation, sweating, circulatory and pilomotor changes. The sensations described above are regarded as those developed in the course of the convulsive spread of the vomiting act through the vegetative nervous system. The second stage, or stage of "emesis," results when the convulsion sweeps out of the vegetative system and involves the muscles of the stomach, esophagus, respiration and the skeletal muscles in general.

THE SIGNIFICANCE OF UROBILOGEN IN THE URINE AS A TEST FOR LIVER FUNCTION

WITH A DESCRIPTION OF A SIMPLE QUANTITATIVE METHOD
FOR ITS ESTIMATION¹

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Although it has long been recognized that the liver has a number of distinct functions, complete knowledge of any of these is still lacking. Especially is it difficult to determine whether any of the functions ascribed to the liver are carried on by this organ alone and not shared by other organs as well. There is far from general agreement in the interpretation of the experimental data available and from which conclusions have been drawn. In the light of this, it follows that any functional test, designed to measure liver abnormality, must be limited in its application and interpreted with great caution in terms of liver function. In any disease of the liver, it is unlikely that all functions are deranged, or at least equally involved, and, furthermore, there is no known single test which measures liver function as a whole. Liver functional tests are comparable then to renal tests, and the problem is to find simple clinical measures, each demonstrating some type of liver abnormality, and all, taken together, allowing of a general statement of liver efficiency. The present paper has to do with the clinical significance of urobilogen in the urine.

The function of the liver first recognized, and, one would assume, most easy of complete explanation, is that of bile formation and excretion. Yet this function, especially with regard to the place of bile formation, and to the relationship between blood destruction and bile pigment formation is far from being definitely established. The commonly accepted belief is that bile pigment is a product of destroyed blood cells, that the transformation occurs in the Kupffer cells of the liver, and that the hepatic cells serve the purpose of excretory cells. This belief is based largely on indirect evidence, chiefly on the chemical relationship between bile and blood pigments, and on the increase in bile pigment following abnormal destruction of blood cells. Strong opposition to the view that bile is formed only from blood cells is expressed by Whipple and Hooper,¹ who state that the feeding of blood does not increase the bile output, whereas carbohydrate feeding causes a marked increase

¹ From the New York University Medical College and Bellevue Hospital

1 Whipple, G H Pigment Metabolism and Regeneration of Hemoglobin in the Body, *Arch Int Med* **29** 711 (June) 1922 Hooper, C W, and Whipple, G H *Am J Physiol* **40** 349 (April) 1916, *J Exper Med* **23** 137 (Jan) 1916

They conclude that their experiments overthrow the belief that bile pigment is formed only as a result of blood destruction Rous and McMaster² criticise this conclusion, and believe that it is unwarranted because of faults in the experimental methods employed

The belief that the liver is the sole seat of bile pigment formation is based on the classic work of Minkowski and Naunyn³ They found that the jaundice occurring in geese, following hemolysis from arsenuretted hydrogen did not occur in hepatectomized geese A later worker, McNee,⁴ has repeated these experiments He found that bile could be detected in the urine of the hepatectomized geese, but only in very small amounts In general, he confirms Minkowski and Naunyn, and goes a step further in assuming that it is the phagocytic Kupffer cells in which the transformation of hemoglobin to bile pigments takes place He admits the possibility of the Kupffer cells in other parts of the body taking part in this transformation, but believes this can occur only to an insignificant degree

A recent contribution to the subject is by Jones and Jones⁵ In a case of paroxysmal hemoglobinuria, they obtained a positive Gmelin test in the blood serum taken from a ligated extremity, some time after exposure to the cold They consider this positive evidence of the formation of bile pigment outside the liver This conclusion can be accepted, however, only when it is shown that a positive Gmelin test is certain proof of the presence of bilirubin

Whipple and Hooper,⁶ working along the same line on dogs, reported that, after cutting off all the blood supply to the liver, hemoglobin injected into the animal is promptly transformed into bile pigment Their experiments, which have been widely quoted, were generally accepted as proving that the liver is not necessary for bilirubin formation Rich,⁷ however, has shown that the method employed by Whipple and Hooper does not shut off, but in fact permits, a very active circulation in the liver In his own experiments, in which he either extirpated the liver, or completely cut off its circulation, there was not a trace of bilirubin in the blood serum, nor the slightest evidence of jaundice, in from one to five hours after the injection of hemoglobin

² Rous, P., and McMaster, P. D. *J. Exper. Med.* **37** 11 (Jan.) 1923
Rous, P., McMaster, P. D., and Broun, G. O. *J. Exper. Med.* **37** 733 (June) 1923, *ibid.* **37** 395 (March) 1923

³ Minkowski and Naunyn *Ikterus durch Polycholie*, Arch f. exper. Path u. Pharmakol. **21** 1, 1886

⁴ McNee, J. W. *Med. Klin.* **28** 1125, 1913, *J. Path. & Bacteriol.* **18** 325, 1913

⁵ Jones, C. M., and Jones, B. B. *Study of the Hemoglobin Metabolism in Paroxysmal Hemoglobinuria*, *Arch. Int. Med.* **29** 669 (May) 1922

⁶ Whipple, G. H., and Hooper, C. W. *J. Exper. Med.* **17** 612, 1913, *Am. J. Physiol.* **42** 256 (Jan.) 1917

⁷ Rich, A. R. *Bull. Johns Hopkins Hosp.* **34** 321 (Oct.) 1923

Opposed to these experiments of Rich are some reported by Mann.⁸ The latter has devised a three stage operation whereby the entire liver may be removed without disturbing the general circulation, and allowing a postoperative period of from two to ten hours, during which time the animal appears normal. Mann states that, within a few hours after hepatectomy, bile pigment, or a substance responding to the tests for bile pigment, appears in the plasma, tissues and urine. He offers no suggestion as to the origin of this substance.

We are unable to explain the difference in results between these two sets of experiments. Mann states that the pigment begins to appear in the urine a few hours after the removal of the liver, whereas Rich's maximum time of experiment was five and a half hours. It is possible that, some hours after removal of the liver, other tissues may become effective as bile formers. Again, there is a possibility of bile escaping into the abdominal cavity during the operation and being later absorbed. Neither explanation seems plausible. We feel, however, that while the question of place of formation of bile pigments is still an open one, the weight of available evidence places the liver as the chief, if not the only, organ concerned in the final process.

Whether or not the liver is the only organ capable of forming bile pigments, the pigments themselves normally eventually pass through this organ into the intestine. The amount of bilirubin in blood serum is minute, one-two hundred fifty thousandths, and its presence can be explained either as an overflow from the liver, from a formation elsewhere, or from an absorption from the small intestine. The daily flow of bile, under suitable experimental conditions, is quite regular. The liver has a large factor of safety in regard to bile excretion, and McMaster and Rous⁹ have shown that an obstruction corresponding to three fourths of the bile ducts may be brought about without the appearance of jaundice.

The bile pigments entering the intestine undergo a gradual transformation on reaching the colon. It has recently been denied that any of the bilirubin is reabsorbed as such. In 1868, Jaffe¹⁰ isolated from the urine and bile a substance with definite spectroscopic properties, which he called urobilin. He also was able to show that this substance showed a characteristic chemical reaction, namely, a green fluorescence, when an alkaline solution was treated with zinc chloride. Vanlair and

⁸ Mann, F. C., and Magath, T. B. Effect of Total Removal of Liver, Collected Papers of the Mayo Clinic 13 200, 1921.

⁹ McMaster, P. D., and Rous, P. J. Exper Med 33 731 (June) 1921.

¹⁰ Jaffe. Beitrag zur Kenntnis der Galleen- und Harnpigmente, Zentralbl f med Wissensch., 1868, p 241, Ueber Fluoreszenz des Harnfarbstoffes, ibid 1869, p 177.

Masius,¹¹ in 1871, obtained from the stool a pigment, stercobilin, which they considered differed slightly from urobilin in spectroscopic relations Maly,¹² at about the same time, succeeded in obtaining from bilirubin, through reduction with sodium amalgam, a pigment corresponding spectroscopically and in chemical reaction to urobilin He called this pigment hydrobilirubin Somewhat later, Muller demonstrated that bilirubin, in hydrogen atmosphere, was transformed by intestinal bacteria into hydrobilirubin Finally, Garrod and Hopkins¹³ showed that urobilin from normal and pathologic urines, from feces, and from bile removed from the gallbladder postmortem is one and the same thing More recently, Hans Fischer and Meyer-Betz¹⁴ and Charnas¹⁵ again took up the study of urobilogen They were able to isolate it from pathologic urines and feces, and proved its identity with hemibilirubin, which Fischer obtained in a 50 per cent yield by reducing bilirubin with sodium amalgam

Jaffe had found that the urobilin content in urine increased on exposure to light and air Disqué¹⁶ was later able to show that, by strong reduction of bilirubin with sodium amalgam and other reducing agents, the chromogen of urobilin, urobilogen, could be obtained By subsequent oxidation, this could be changed to urobilin

The chemical structure of urobilogen, from the work of Nencki,¹⁷ contains a pyrrol nucleus Hans Fischer¹⁸ later established the chemical formula of $C_{33}H_{42}O_6N_4$ According to Fischer and Roese,¹⁹ it has four pyrrol nuclei in common with hemin and bilirubin Neubauer,²⁰ in 1903, showed that Ehrlich's reagent, dimethylamidobenzaldehyd, in hydrochloric acid solution, gives a typical red coloration of urobilogen solutions This reaction is one common to pyrrol groups

ORIGIN OF UROBILOGEN

Since the publication of Friedrich Muller on the subject, the enterogenous origin of urobilogen has been generally accepted Briefly

¹¹ Vanlair and Masius Ueber einen neuen Abkommling des Gallenfarbstoffes im Darminhalt, Zentralbl f med Wissensch, 1871, p 369

¹² Maly Kunstliche Umwandlung von Bilirubin in Harnfarbstoff, Zentralbl f med Wissensch, 1871, p 849

¹³ Garrod and Hopkins Preparation of Urobilin, J Physiol **20** 112, 1896, ibid **22** 451, 1898

¹⁴ Fischer, H., and Meyer-Betz, F. Ztschr f physiol Chem **75** 232, 1911, ibid **75** 339, 1911 Munchen med Wchnschr **59** 799, 1912

¹⁵ Charnas Biochem Ztschr **20** 401, 1909

¹⁶ Disqué Ueber Urobilin, Ztschr f physiol Chem **2** 1877, 1878

¹⁷ Nencki and Zaleski Berl Berichte **34** 997, 1901

¹⁸ Fischer, Hans Ztschr f physiol Chem **73** 204, 1911

¹⁹ Fischer and Roese Ztschr f physiol Chem **89** 25, 1914

²⁰ Neubauer, Otto Ueber die neue Ehrlichsche Reaktion mit Dimethylamidobenzaldehyde, Sitzungsb d Gesellsch f Morphol u Physiol in Munchen **32**, 1903

stated, this conception is as follows Bilirubin, entering the intestine, undergoes gradual changes, and, eventually, in the large intestine, by means of bacterial decomposition, becomes transformed into urobilogen. Maly was first to call attention to the action of bacteria on bilirubin. Later, Friedrich Muller²¹ obtained urobilogen by bringing bilirubin in contact with peptone solution and putrefactive bacteria. Beck²² obtained similar findings by mixing sterile bile with various strains of micro-organisms. The urobilogen thus formed in the intestine is eliminated, in the main, with the feces. Some of it undergoes intestinal absorption and is carried to the liver, there to undergo further changes, part of it, however, is eliminated in the urine unchanged. A striking support of this conception is afforded by a case reported by Muller. He administered to a patient, with a complete biliary obstruction and with no traces of urobilogen in the urine, large quantities of bile. Within twenty-four hours, urobilogen appeared in the feces, and within forty-eight hours in the urine. Further support of this view is the fact that in the first days of the new-born, no urobilogen is found in the meconium, also that, in active purgation, the urobilogen disappears and unchanged bile pigment is found in the feces.

There has been some opposition to the views of Muller. In this country, Whipple and Hooper,¹ particularly, have questioned the intestinal production of urobilogen and its absorption into the portal circulation. In fact, only as recently as 1922, they stated, "There is not a shred of evidence, chemically or experimentally, to indicate that stercobilin is ever absorbed from the intestine." And again, "The intestinal absorption of stercobilin should be discredited until some positive evidence of such absorption is brought forward."

Ladage,²³ after the administration of bilirubin by mouth, obtained a marked increase in urobilin excretion in the stool, and a slight but definite increase in the urine. On giving 100 mg of urobilin by mouth, he obtained a marked increase of urobilogen in the urine. It seems to us that this is positive evidence of intestinal absorption of the substance.

In dogs with biliary fistula and common duct occlusion, Fischler²⁴ has found urobilogen in the bile coming through the fistula. Wilbur and Addis²⁵ have reported similar findings in animals as well as in men.

21 Muller, Friedrich Ztschr f klin Med **12** 45, 1887, Verhandl Kong f inn Med, 1892, p 118

22 Beck, A Ueber die Entstehung des Urobilins, Wien klin Wchnschr **35**, 1895

23 Ladage, A A Bijdrage tot de kennis de Urobilinurie, Dissertation, Leyden, 1899, quoted by Fischler (Footnote 24)

24 Fischler, F Physiologie und Pathologie der Leber, 1906

25 Wilbur, R L, and Addis, T Urobilin Its Clinical Significance, Arch Int Med **13** 235 (Feb) 1914

with cholecystostomy operations Schneider,²⁶ and Jones,²⁷ working with duodenal bile, also have found urobilogen. Jones⁵ reports an increase in the urobilogen of the duodenal bile in a case of paroxysmal hemoglobinuria within only a few hours after the production of an intravascular hemolysis of a peripheral vessel. These workers, as well as Hayem of the French school, believe in an extra-enterogenous origin of urobilin, and that the liver itself possesses the faculty of forming this substance.

Considering, therefore, these conflicting views, a series of experiments were undertaken by us, which are herein reported. We found, on the whole, no evidence pointing to an extra-enterogenous formation of urobilogen. In the main, our experiments substantiate Muller's conception. We feel that this fact is an important one since the usefulness of the urobilogen test, as an evidence of liver disturbance and as an aid in the clinical differentiation between various types of icterus, depends entirely on the enterogenous origin of urobilogen.

It is quite possible to explain the presence of urobilogen in the liver bile, as we shall see later, as the result of an infection in the biliary passages on the one hand, and, on the other, as a return excretion of the absorbed intestinal urobilogen.

The belief that urobilogen may be formed in the kidney, through a reduction occurring in that organ, appears to have been definitely disproved.

METHODS OF ESTIMATION

The methods commonly used to determine the presence of urobilogen and urobilin are (1) fluorescence in the presence of zinc salts, (2) spectroscopic absorption bands, (3) production of a red color by the addition of Ehrlich's aldehyd reagent.

(1) The fluorescent test is a test for urobilin only. While the fluorescence of urobilin, in the presence of zinc salts, was shown by Jaffe, in 1868, yet its practical application as a test is due to Schlesinger,²⁸ who, in 1903, introduced the saturated alcoholic solution of zinc acetate. This, in a slightly alkaline reaction, gives a green fluorescence with urobilin. The test is a very delicate one. In working with pure solutions of urobilin, he could obtain reactions up to 0.002 per cent (1:50,000 dilution). Fischler, in 1906, applied this test to the quantitative estimation of urobilin, after having converted the urobilogen to urobilin by direct exposure to sunlight. In comparing the delicacy of this test to the spectroscopic disappearance of the absorption bands, he found it twenty-two and one-half times as sensitive (0.002 per cent as compared to 0.045 per cent).

26 Schneider, J P. Anemia, Arch Int Med **17** 32 (Jan.) 1916.

27 Jones, C M. Blood Pigment Metabolism and Its Relation to Liver Function, Arch Int Med **29** 643 (May) 1922.

28 Schlesinger, H. Zum klinischen Nachweis des Urobilins, Deutsch med Wschrnschr **32** 561, 1903.

The quantitative fluorescence test was later simplified by Marcussen and Hansen²⁹ and again by Adler³⁰ who converted the urobilogen into urobilin by the addition of a three per cent solution of iodine, according to Ladage,²³ and by Conner and Roper³¹ Adler employed the saturated alcoholic solution of zinc acetate to carry on his dilutions. He calculates his final results in terms of milligram of urobilin.

(2) The spectroscopic method dates back to Gerhardt,³² who, in 1889, used the spectrophotometer, employing Vierordt's tables to study the light extinction of solutions of urobilin as compared to normal urine. Since then, the spectroscopic method has had a very wide application, being used also in the Charnas¹ and Brugsch and Retzlaff³³ methods of urobilogen and urobilin estimations.

Wilbur and Addis,² in this country, in 1914, introduced a very practical quantitative spectroscopic method for estimating the combined urobilogen and urobilin. They make use of Charnas' principle of reading the urobilogen after the addition of Ehrlich's reagent, estimating at the same time the urobilin in the acid solution, which gives high readings and a better constant. The test is performed as follows. To 10 c.c. of urine out of a twenty-four hour specimen is added 10 c.c. of a saturated alcoholic solution of zinc acetate, this is filtered. To 10 c.c. of the filtrate, 1 c.c. of Ehrlich's reagent is added. The spectroscopic reading is made anywhere from fifteen minutes to an hour afterward. "The filtrate is gradually diluted with tap water until first one and then the other bands of light absorption have disappeared when the full amount of light enters the spectroscope, but are still visible when the light is partly shut off." The dilutions required give the value for 5 c.c. of urine. Multiplying this figure by the number of 5 c.c. in the total twenty-four hour urine, one obtains the total figure of urobilogen and urobilin in the twenty-four hour specimen.

(3) Ehrlich's aldehyd reaction, which consists of a red condensation product was first introduced by Otto Neubauer, in 1903. The reagent is composed of 2 gm of paradimethylamido benzaldehyd in 100 c.c. of 20 per cent hydrochloric acid solution. This test for urobilogen is very sensitive. According to Fischer, it will still give a reaction with a dilution of one part of urobilogen to 640,000 parts of water.

Brugsch and Retzlaff, in 1912, and Flatow and Brunell, in 1913, attempted quantitative estimations by using colorimetric standards, one employing a Bordeaux red solution, and the latter, phenolphthalein.

AUTHORS' METHOD

The quantitative test devised by the authors is dependent on Ehrlich's aldehyd reaction, and consists of a series of dilutions of the urine carried to a point where no further reaction takes place. The end-result is read off where the faintest pink is still discernible. The reading is made by looking through the mouth of the test tube, holding the tube obliquely against a white background. Dilutions may be made with plain tap water.

Following are the details of the method. First 1 c.c. of Ehrlich's reagent is added to the whole urine, and the strength of the reaction

29 Marcussen and Hansen, S J Biol Chem 36 381 (Nov) 1918

30 Adler, A Deutsch Arch f klin Med 138 309 (Feb) 1922, ibid 140 302 (Nov) 1922

31 Conner, L A, and Roper, J C The Relations Existing Between Bilirubinemia, Urobilinuria and Urobilinemia, Arch Int Med 2 532 (Jan) 1909

32 Gerhardt, C Ueber Urobilinurie, Wien med Wchnschr 27 577, 1877

33 Brugsch and Retzlaff Ztschr f exper Path u Therap 11 508, 1912

noted by the rapidity and intensity of its development. The full development requires from one to three minutes. In strong urobilogen concentrations, a deep red color comes on promptly. One learns quickly to gage the presence of abnormal quantities from this qualitative test, and dilutions are not carried out if the color remains a light red within the time allowed, as here one deals with normal values. If, however, the original reaction indicates an increase, we then make a series of dilutions by adding 1 c.c. of the urine to 20, 30, 40, 50, 100, 200 c.c. of water, or more. From 10 to 15 c.c. of each dilution is placed in test tubes, and to each is added 1 c.c. of Ehrlich's reagent. The reading is made after from three to five minutes so as to allow the full development of the color. The last dilution must be the faintest pink discoloration, and the quantitative determination is expressed in terms of the greatest dilution of the urine in which the pink color is present, 1:10, 1:50, etc. If the color does not appear within five minutes, it may be disregarded. If the tap water is too cold, the reaction may be somewhat retarded. Care should be taken that the color is a genuine pink and not a yellowish brown, as is often found in urines containing bile or in concentrated urines. The test is preferably carried out in daylight. It is best not to make a reading in the bright sun as the shining rays have a tendency to intensify the color. Artificial light also does this to some extent.

In carrying out the test, we have disregarded entirely the estimation of urobilin, as this substance is never found in the freshly voided urine and forms only very slowly if the urine is kept away from the sunlight. We have made repeated observations on the daily loss of urobilogen, and have found that, if we allowed urines containing known amounts of urobilogen to stand for twenty-four hours, away from the strong light and in the cold, there was a loss, after twenty-four hours, of one-fifth the total urobilogen. If the exposure was continued for another twenty-four hours, there was a loss of another fifth, and so on, approximating a fifth or slightly less for every twenty-four hours.

We prefer to examine single fresh specimens rather than total twenty-four hour specimens, as we may thus find at least one specimen with a high urobilogen content. Such increase, if occurring even once a day, signifies an existing pathologic condition.

ADVANTAGES OF METHOD

In comparing our method with the Wilbur and Addis spectroscopic method as to delicacy and final end-results, we found that we could carry our dilution five or six times as high as the disappearance of the spectroscopic bands would indicate. Through the courtesy of Dr. Gettler of Bellevue Hospital, comparisons between our test and the Wilbur-Addis test were made. In one urine, for instance, it was found that the spec-

troscopic bands were still visible at a 1:30 dilution and were totally absent at a 1:40 dilution (This would mean a 1:60 dilution, as only half the original solution was urine) In our test, however, the dilution could be carried to 1:350 before the final color disappeared, showing our test to be six times as delicate

The quantitative fluorescent test possesses several elements of uncertainty (a) the variability of the fluorescence, the intensity varying with fine shades of differences in the reaction, thus often interfering with the end-result, (b) the conversion of urobilogen into urobilin by oxidizing agents such as iodin or sunlight, wherein uncertainty arises as to whether the entire urobilogen has been thus changed The sunlight always causes some loss in the urobilin (c) Some loss in the urobilin when present in large amounts also takes place in the precipitation with the alcoholic solution of zinc acetate (d) Special light is required in reading the final dilutions

Our test also is more delicate than the fluorescent test It is very simple, and does not require any complicated chemical procedures or special apparatus It requires only a few minutes for its completion and can be done in any office, irrespective of the kind of light

The examination of urobilogen in the stool presents difficulties due to interferences from indol and skatol These substances give a similar reaction with Ehrlich's aldehyd reagent, and show similar spectroscopic absorption bands in alcoholic extractions It is therefore necessary first to remove these putrefactive substances This is best done by rubbing the stool in a mortar with petroleum ether and centrifugating Several such extractions are made until the clear supernating petroleum ether no longer gives the Ehrlich's reaction Of the remaining feces, alcoholic extractions are made until all the urobilogen is taken up Using a definite weight of feces and a definite amount of alcohol, the urobilogen can be quantitatively estimated in similar dilutions

ANIMAL EXPERIMENTS

Our experiments were undertaken with the objects (1) to make clear to ourselves the significance of an increase in urobilogen, particularly the relation of liver damage to urobilogen, and (2) to study the rôle of the intestine in the formation of urobilogen, i e, the necessity of a flow of bile into the intestine for its formation, particularly in view of the many different opinions as to the mode and place of origin of this substance We have repeated some of Fischler's experiments and added others of our own

Female dogs were used for this purpose, the urine being obtained by catheterization and examined for urobilogen immediately after with-

drawal In the normal dog, urobilogen appears in the minutest traces and the Ehrlich's aldehyd reaction gives a faint pink color In a dilution of 1:10 the result is usually negative

To produce the liver damage, we have used a number of known liver poisons, but have confined ourselves especially to chloroform because of its certainty of action³⁴

After a preliminary period of observation during which, in some experiments, food was withheld from the animals for a few days,³⁵ chloroform was given by inhalation, in an amount sufficient to induce surgical anesthesia, and continued over a period of from one half to two hours (usually between one and one half and two) The urine was examined at intervals during the following days In some of these experiments, a phenoltetrachlorphthalein test was made while the chloroform effects were present, to serve as a check and allow of a comparison of the two tests The dye was injected intravenously, 5 mg per kilogram of body weight, and the amount remaining in the serum determined at the end of one hour³⁶ We also have made a few determinations of the effects of carbon tetrachlorid on urobilogen excretion This substance has been shown, by Lamson,³⁷ to be toxic to the liver and to affect markedly phenoltetrachlorphthalein excretion Some typical protocols are given in Table 1

DISCUSSION OF EXPERIMENTAL RESULTS

The experimental results we have cited show that whenever the liver is damaged by chloroform there results a decided rise in the urinary urobilogen The rise in terms of dilution may vary from 1:50 to 1:1,000, and is undoubtedly in proportion to the degree of liver damage When carbontetrachlorid is administered prior to the chloroform, the effect is intensified The urobilogen rise commonly occurs on the day following the chloroform inhalation, although, in some instances, it may be delayed or require several inhalations before the damage becomes evident The return to the normal occurs abruptly, from which the inference may be drawn that the functional activity, once started, becomes restored with great promptness

In the experiments with carbontetrachlorid, in Dogs 3 and 5, both the urobilogen and phenoltetrachlorphthalein test were used simulta-

34 Davis, N C, and Whipple, G H Influence of Drugs and Chemical Agents on Liver Necrosis of Chloroform Anesthesia, *Arch Int Med* **23** 636 (May) 1919 Whipple, G H, and Speed J Biol Chem **18** 447, 1914

35 Whipple, G H, and Speed J Biol Chem **18** 612, 1914

36 Rosenthal, S M J Pharm & Exper Therap **19** 385 (June) 1922, New Method of Testing Liver Function with Phenoltetrachlorphthalein, J A M A **79** 2151 (Dec 23) 1922

37 Lamson, P D, and McLean, A J Toxicity of Carbontetrachlorid, J Pharm & Exper Therap **31** 237 (May) 1923

neously in order to determine how these two tests compare with the same liver damage. We find that the results of the two tests are not parallel, and that the liver function appears to be altered more in respect to the dye excretion than as regards the urobilogen.

TABLE 1—*Typical Protocols*

	Date	Chloroform Carbontetrachlorid	Urobilogen in Urine	Bile in Urine	Phenoltetra chlorphthalein
Dog 8	Jan 16		Traces		
	Jan 17	Carbontetrachlorid, 50 c.c.	Traces		
	Jan 18	Chloroform, 1 hour 50 minutes	Traces		
	Jan 19		Traces		
	Jan 21	Chloroform, 1½ hours	1 30		
	Jan 22		1 100		
	Jan 23		1 1000	++	
	Jan 24		1 500	+	
Dog 10	Jan 25		1 10		
	March 1		Traces		
	March 2	Chloroform, 1½ hours	Traces		
	March 3		1 150		
	March 4		1 75		
Dog 7	March 5		Traces		
	Jan 29	Chloroform, 1½ hours	Traces		
	Jan 30		1 50		
	Jan 31		1 75		
Dog 5	Feb 1		Traces		
	Dec 10		Traces		
	Dec 11	Carbontetrachlorid, 75 c.c.	Traces		
	Dec 12		1 25		
	Dec 13	Carbontetrachlorid, 50 c.c.	Traces	+	7% after 1 hour
	Dec 14		1 30		
	Dec 15		1 30		
	Dec 19	Chloroform, 2 hours	1 30		1% after 1 hour
	Dec 20		1 300	++	4% after 1 hour
	Dec 21		1 250	+	
	Dec 22		1 100	+	
	Dec 23		1 75	+	
	Dec 24		1 50		
	Dec 25		1 30		
Dog 6	Dec 28	Chloroform, 1½ hours	Traces		
	Dec 29		1 50	+	
	Dec 30		1 40		
	Dec 31		1 50		
	Jan 2		Traces		
Dog 4	Dec 24		Traces		
	Dec 26	Chloroform, 2 hours	Traces		
	Dec 27	Chloroform, 2 hours	1 60	+	10% after 1 hour
	Dec 28		1 50	+	
	Dec 29		1 50	+	
	Dec 30		1 100		
	Dec 31		Traces		
Dog 2	Dec 3		Traces		
	Dec 4	Chloroform, 2 hours	Traces		
	Dec 5	Chloroform, ½ hour	Traces		
	Dec 6	Chloroform, ¼ hour	1 35		
	Dec 7		1 75		6% after 1 hour
	Dec 8		1 50		
	Dec 9		Traces		
	Dec 10	Chloroform 1 hour	Traces		
	Dec 11	Chloroform 1½ hours	Traces		
	Dec 13		1 125		
	Dec 14		Traces		

Somewhat similar quantitative differences are seen when the liver is damaged with chloroform. The evidence presented points then to these two tests as being supplementary and not indicative of a single functional disturbance. While our experiments are not conclusive on this

point, we feel that the purely excretory function shown by the phenoltetrachlorphthalein test differs from that relating to the urobilogen. Similar differences will also be shown in our clinical material.

LIGATION AND EXCISION OF THE COMMON BILE DUCT

After having established the relation between liver damage and the urobilogen output, with a normal flow of bile into the intestine, we then took up the second point for investigation, which concerns the rôle of the intestine in the formation of urobilogen, or the dependence of the urinary urobilogen on the flow of bile into the intestine. In determining this point, we have ligated the common bile duct in the animals that had been previously tested out as to the effect of chloroform anesthesia on the output of urobilogen. We have used the dogs reported in the preceding experiments after their urinary urobilogen had returned to normal. The common bile duct was ligated in two places and a segment of the duct was resected between the two ligatures. In Dog 8, a biliary fistula also was made. After the animals had sufficiently recovered from the operative procedure, chloroform was again administered, and the effects noted. An anastomosis between the gallbladder and duodenum was made in Dog 7, ten days after the ligation and excision of the common duct. Fresh pig's bile was administered by mouth to Dog 5, the second day after the ligation of the common duct, and continued for several days. The protocols of the experiments are given in Table 2.

We feel that the experiments given in Table 2 clearly substantiate the intestinal formation of urobilogen, and show that without the presence of bile in the intestine, urobilogen is not formed, even though the liver is subjected to the same degree of damage as before. As is seen in Dogs 10 and 6, after the ligation of the common duct, repeated chloroform administrations do not cause the appearance of any urobilogen. In Dog 7, when the flow of bile was reestablished in the intestine by an anastomosis between the gallbladder and the duodenum, the urinary urobilogen promptly made its appearance. Similarly, in Dog 5, when bile was fed by mouth, the urobilogen also appeared in the urine.

In this connection, we wish to cite a case which presents some analogy to our experimental work on Dog 7. A patient, aged 40, developed jaundice, in December, 1923. The jaundice increased, becoming intense in January, with an acholic stool and evidence of complete obstruction of the bile duct. Urobilogen, at this time, was totally absent from the urine. In February, an exploratory operation was performed and a hard mass found infiltrating the head of the pancreas, the gallbladder being dilated. An anastomosis between the gallbladder and stomach was made. A week after the operation, the jaundice had greatly diminished, and the stools became brown. The urobilogen was positive in a 1:40 dilution.

Only in Dog 8, with a gallbladder fistula, in which a severe infection took place spreading throughout the liver and later to the other abdominal organs, did the urinary urobilogen rise after chloroform anesthesia. The appearance of urobilogen, in this dog, with an occlusion of the common duct might cause one to believe in the hepatic origin of the substance. On closer study, however, it can be explained on the basis of an ascending infection along the biliary radicles. The same process of decom-

TABLE 2.—Protocols of Experiments in Which Ligation and Excision of Common Bile Duct Was Done

	Date	Chloroform, Carbontetrachlorid	Urobilogen in Urine	Bile in Urine
Dog 10	March 2	Chloroform, 1½ hours	Traces	
	March 3		1 150	
	March 10	Common bile duct ligated	Traces	
	March 12		0	++++
	March 13	Chloroform 1½ hours	0	++++
	March 14	Chloroform 1½ hours	0	++++
Dog 7	March 15		0	++++
	Jan 29	Chloroform, 1½ hours	Traces	
	Jan 30		1 75	
	Feb 15	Bile duct ligated and excised, also biliary fistula	Traces	
	Feb 19		0	
	Feb 20	Chloroform, 1½ hours	0	
	Feb 21		0	++
	Feb 23		0	++++
Dog 6	Feb 25	Anastomosis between gallbladder and duodenum	0	++++
	Feb 27		1 40	+++
	Dec 30	After chloroform 2 hours	1 100	
	Dec 31		Traces	
	Jan 2	Bile duct ligated and excised	Traces	
	Jan 3		1 40	
	Jan 5	Chloroform, 1½ hours	0	
	Jan 6		0	
Dog 5	Jan 7	Chloroform 1½ hours	0	
	Jan 8	Chloroform 1 hour	0	
	Dec 25	After chloroform	1 300	
	Jan 2	Common bile duct ligated and resected	Traces	
	Jan 3	75 c.c. fresh pig's bile by mouth		
Dog 8	Jan 4	50 c.c. fresh pig's bile by mouth		
	Jan 5		1 25	
	Jan 23	After chloroform	1 1 000	
	Jan 30	Common duct ligated and excised gallbladder fistula	Traces	
	Jan 31		0	
	Feb 1		0	
	Feb 2		0	
	Feb 3		0	
	Feb 4		0	
	Feb 5	Chloroform, 1½ hours	0	
	Feb 6		1 50	

position of bilirubin which takes place in the intestinal canal by the bacterial flora may take place in the liver substance itself, within the biliary radicles. Such urobilogen may then be excreted with the bile, and, if the parenchyma of the liver also is damaged following the prolonged chloroform anesthesia, then the urobilogen escapes into the general circulation.

In our animals with biliary fistula, no urobilogen could be found in the fistula bile within the first few days after the operation. Later, however, when infection took place, as in Dog 8, urobilogen made its

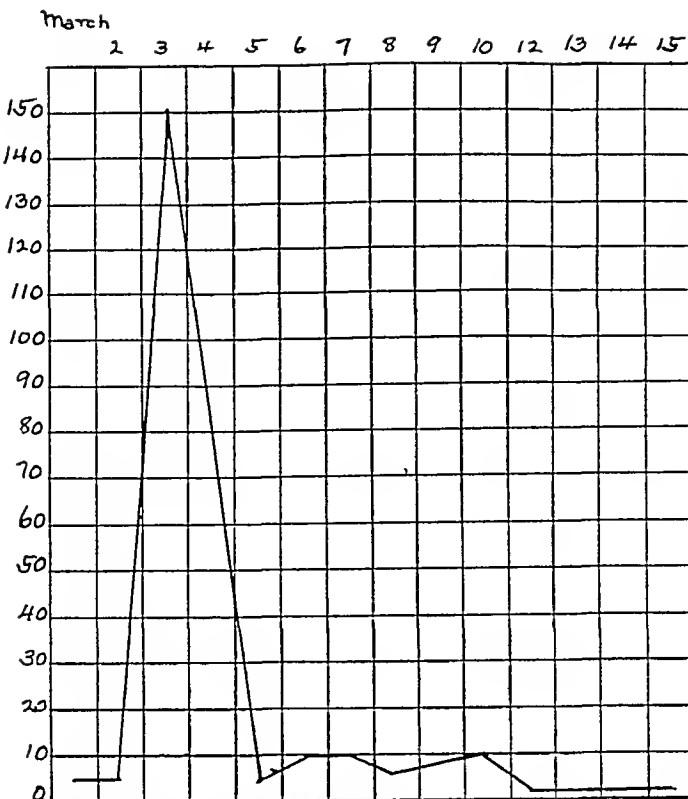


Chart 1 (Dog 10) —Urobilogen elimination in liver damage before and after exclusion of bile from intestine. The ordinates, in this and the following charts, represent the highest dilutions of the urine at which the urobilogen test was still positive. March 2, chloroform anesthesia was given for one and three-fourth hours, urobilogen rose from traces to 1 150 within twenty-four hours, it came down to normal within forty-eight hours. March 10, the common bile duct was ligated, urobilogen came down to zero, March 12. Chloroform was again administered, March 13, and repeated on the 14th, urobilogen remained at zero.

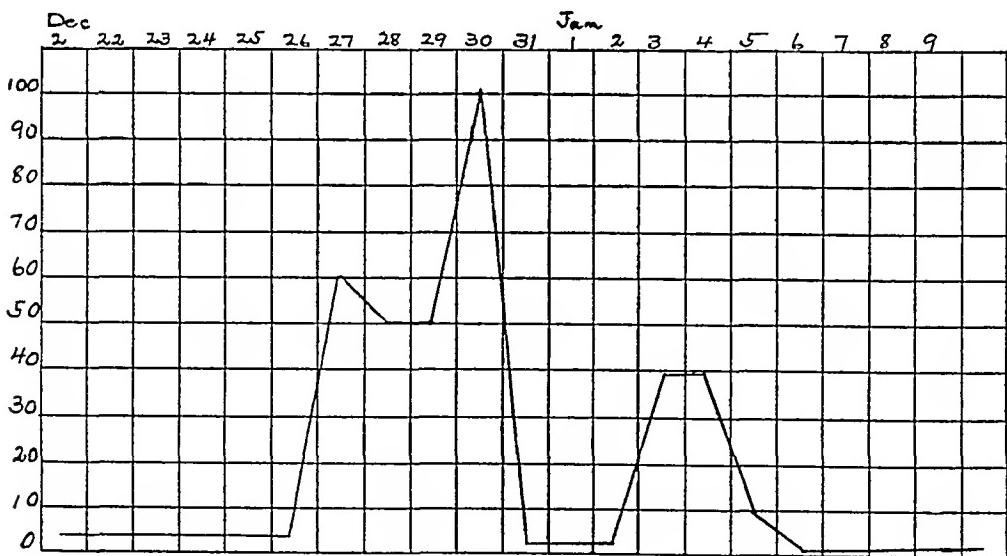


Chart 2 (Dog 6) —Similar effect to that shown in Chart 1 (Dog 10). December 26, chloroform anesthesia was given for two hours, urobilogen rose from traces to 1 60. December 27, chloroform was again repeated for two hours, urobilogen rose to 1 100, December 30, and fell to normal on the 31st. January 2, the bile duct was ligated and excised. There occurred a temporary rise of urobilogen lasting two days, probably due to the urobilogen content in the intestinal canal. Chloroform anesthesia was given January 5, urobilogen down to zero. Chloroform was repeated, January 7, and 8, urobilogen remained at zero.

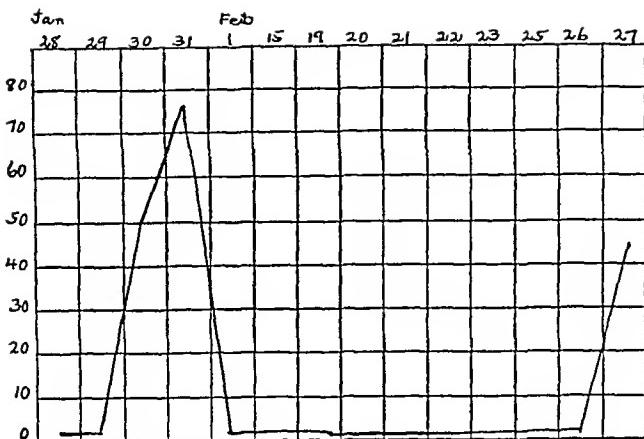


Chart 3 (Dog 7) —Urobilogen elimination in anastomosis between gallbladder and duodenum after exclusion of bile from intestine January 29, chloroform anesthesia was given for one and three-fourth hours, urobilogen rose to 1 75 within two days, and fell to normal on the third day February 15, the common bile duct was ligated February 20, chloroform was administered for one and three-fourth hours, urobilogen fell to zero February 25, anastomosis between gallbladder and duodenum was made, February 27, urobilogen rose to 1 45

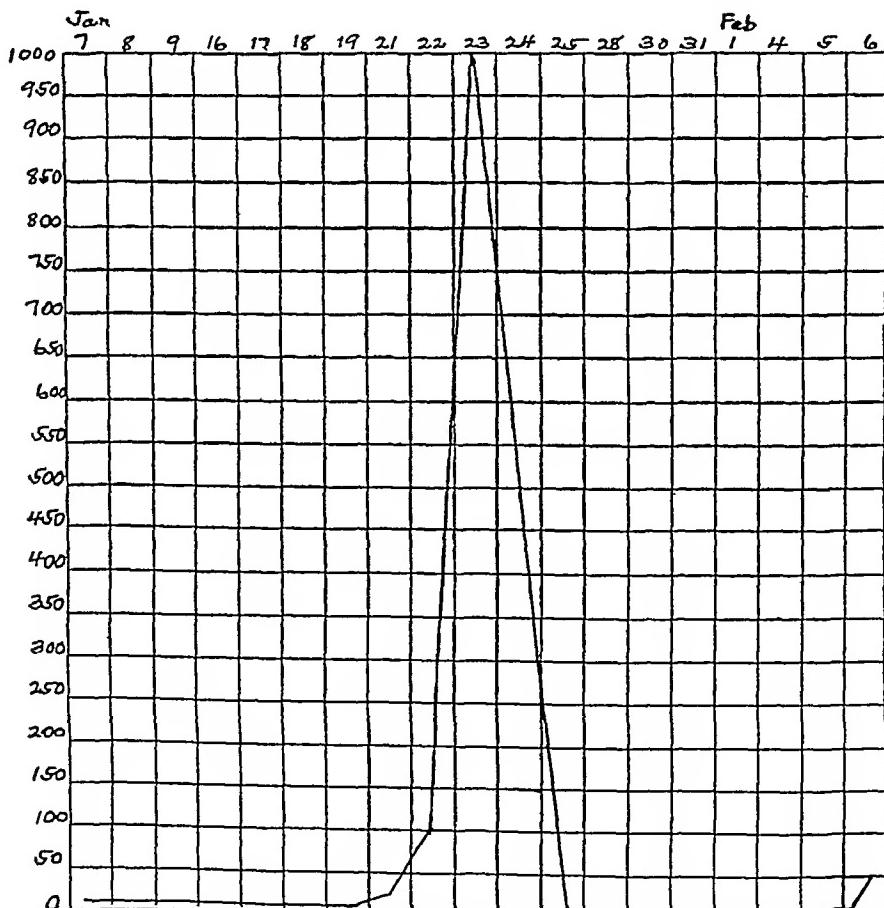


Chart 4 (Dog 8) —Urobilogen elimination in infection of biliary tract with exclusion of bile from intestine Carbontetrachlorid and two sessions of chloroform were administered, between January 17 and 21, urobilogen rose, January 23, from traces to 1 1,000, it came down to normal, January 25. The common duct was ligated and a gallbladder fistula made, January 30, urobilogen fell to zero. There was severe infection of the liver and peritoneum February 5, chloroform was given, urobilogen rose, on the 6th, to 1 50

appearance Dog A of Wilbur and Addis' experiments also illustrates that a low grade infection can occur through the biliary fistula, which may lead to pronounced liver changes This dog with biliary fistula and common duct ligation eliminated large amounts of urobilogen At postmortem examination, a marked cirrhosis of the liver was found

We have been unable to find any corroborative evidence in support of the formation of urobilogen by the liver parenchyma The most striking phenomenon is the absence of urinary urobilogen in the animals with common duct ligation, in spite of the fact that the liver was subjected to considerable damage by repeated chloroform anesthesias If urobilogen is a product of the liver cell itself, one should expect to find it in the urine in the cases with common duct ligation, in which all the secretions and excretions of the liver, being dammed back into the general circulation, have only one avenue of escape Its absence from the urine speaks, therefore, against a hepatic origin

PRESENCE OF UROBILOGEN AND UROBILIN IN THE INTESTINE IN OCCLUSION OF THE COMMON DUCT

In examining the stools in common duct obstructions, we found, after careful extraction with petroleum ether, small quantities of urobilogen even after a preliminary flushing of the bowels with purgatives and cleansing enemas We feel that the presence of these small quantities must be explained on the basis of an elimination of bilirubin from the blood serum into the intestine, and there changed to urobilogen The scybala often presented a thin outer layer of dark brown which covered a central acholic portion In making separate examinations of the central and outer layers, we found that the inner portion was entirely free from urobilogen and urobilin, but that the pigmented outer portion gave positive reactions This tends to show, in these cases with saturation of bile in the plasma, that bilirubin is eliminated into the intestinal canal, coating the outer layer of the feces, and is there changed by bacterial putrefaction

We cannot agree with Wilbur and Addis in the belief that these substances are formed in the serum and, as such, eliminated into the intestinal canal The readiness with which urobilogen is excreted by the kidney is well known, and the question always arises why, in common duct obstruction, if urobilogen is formed in the blood stream, it is never found in the urine The assumption, therefore, of an intestinal excretion is not plausible

CLINICAL CONSIDERATIONS

Urobilogen is a normal constituent of urine in man It is present in smallest amount in the morning urine, or may be absent altogether It rises somewhat in the afternoon and evening In constipated individuals

with increased putrefactive changes in the large bowel, the quantity of urobilogen rises above the normal. Urobilin never appears in the freshly voided urine. Even in pathologic urines in which the urobilogen rises to abnormally high figures, urobilin is seldom, if ever, found, and when it is present it occurs in negligible traces.

Using our method of estimation, we found normally urobilogen in the morning urine in amounts which failed to give a reaction if the urine was diluted more than 1:10. During the afternoon and evening, the average maximum use of urobilogen was 1:20. Marcussen and Hansen,²⁹ using the fluorescence method, report similar findings.

In a series of more than 1,000 ambulatory patients, the routine examinations of the urine revealed, in more than 90 per cent anywhere from traces to positive 1:20 dilutions. The remainder presented pathologic conditions relating to the biliary or intestinal tract, to the cardiovascular or hemopoietic system.

A group of 125 medical students also were examined. In seventy-five of these, specimens were obtained in the forenoon, and in the remaining fifty in the afternoon. Seventy-two of the forenoon urines were below 1:20, most of them being about 1:10. One was 1:25, one 1:50, and one was discovered with a very high urobilogen reading of 1:350. The afternoon group corresponded in the main with the morning one with the exception that the figures approached more nearly to 1:20. One of these showed 1:40 and one 1:50. Of the total, 96 per cent gave readings below 1:20.

The elimination of urobilogen also presents in pathologic states great variations between the night and day output. It is always lowest during the night and early morning hours. During the day, the amounts may also vary, sometimes from hour to hour. Wilbur and Addis quote a case of bronze diabetes, which, while showing great irregularities in the output of urobilogen during the day, was always constant in eliminating the lowest quantities by night. If, however, this patient remained up and took his meals during the night and slept in the daytime, then the condition became reversed, the amount excreted during the night being much larger than during the day.

Saillet³⁸ suggests a relation of these variations to the process of digestion and general body metabolism. We may compare the mobilization of the urobilogen by night to the same process which takes place in a deficient kidney function, in which, during the night, the kidney continues to eliminate the excess of solids which it was incapable of eliminating during the day. So the liver during the resting period, when metabolic processes associated with digestion and general body activity are at a standstill, can attend to its retarded functions. The daily variations also must be explained on similar digestive and other

functional interferences, the escape of the excess of urobilogen into the general circulation and into the urine always being highest in the afternoon when metabolic processes are at their highest. These variations are not dependent on changes in the excretory function of the kidney, and do not run parallel with changes in the specific gravity of the urine. Hourly observations of changes, often amounting to twice the amount of urobilogen, would show a variation of only one or two points in specific gravity, thus showing, furthermore, its independence of urine concentration.

DIAGNOSTIC SIGNIFICANCE

Hildebrand was the first to note the numerous instances in which urobilogen appeared in the urine in increased amount. In fact, the frequency of this occurrence in a large variety of conditions has for the time detracted from its usefulness and has led even such observers as Friedrich Muller to express some doubt as to its diagnostic value. In later years, however, a great deal of clinical study has been made, particularly by Eppinger,³⁹ who grouped its pathologic occurrence as follows: (1) diseases of the liver, (2) hemolytic diseases, (3) cardiac diseases, (4) intoxications and (5) infectious diseases.

This grouping, however, may be reduced to two main classifications: (1) hepatic and biliary diseases, and (2) hemolytic diseases. All conditions in which urobilogen appears in increased amounts can be classed under one or the other of these two groups, or a combination of the two.

(1) *Diseases of the Liver and Biliary Tract*—In this group are catarrhal jaundice, cholangitis, acute yellow atrophy, hepatic cirrhosis, chronic passive congestion of the liver associated with chronic endocarditis, especially in the state of chronic decompensation, liver abscess when the suppurative process is generalized but not a solitary lesion, miliary tuberculosis, primary carcinoma of the liver, metastasis producing a general carcinomatosis of the liver but not localized nodular areas, toxic states, such as eclampsia, toxic pregnancies and later stages of tuberculosis, intoxication resulting from the intake of large amounts of alcohol, and also infections such as scarlet fever and measles.

(2) *Hemolytic Diseases*—Among these are grouped hemolytic icterus, pernicious anemia, septic states, malaria, lead poisoning and other hemolysis produced by poisons such as antifebrin, sulphonal and mushrooms. Here it occurs as the result of marked increase in blood destruction with an increased pigment formation, associated also with liver involvement. Minot⁴⁰ has shown that 40 per cent of pernicious anemia patients during life present a large liver. A pathologic state

39 Eppinger, Hans. Die Hepato-Lienalen Erkrankungen, 1920.

40 Minot, C. R. Oxford Med. 2 623, 1920.

of the liver can be demonstrated at necropsy in almost all cases presenting blood destruction, the liver changes often going hand in hand with the changes occurring in the spleen

(1) DISEASES OF THE LIVER AND BILIARY TRACT

Catarrhal Jaundice—The occurrence of urobilogen in excessive amounts is a constant phenomenon in catarrhal jaundice. While it is not present in all stages of the disease, as will be shown later, yet it invariably makes its appearance at one time or another during its course. This forms a marked distinguishing feature from the obstructive jaundice, in which the interference of the bile flow results from outside pressure on the common or hepatic ducts. In the obstructive jaundice conditions, urobilogen never appears in the urine.

Its occurrence in catarrhal jaundice indicates an acute parenchymatous change in the liver cells somewhat analogous to the changes produced by prolonged chloroform anesthesia. We cannot, therefore, regard the disease in the light of the old Virchow conception of an obstruction of the common duct due to a mucous plug. The flow of bile into the duodenum is always present. It may be scanty at times but it is never completely interrupted.

Out of a series of seventeen cases of catarrhal jaundice here reported, twelve were intubated with a duodenal tube. Bile was found in all cases, the pigment varying from scanty to normal amounts. The introduction of magnesium sulphate, according to the Meltzer-Lyon method, seldom yields, in these cases, the typical dark brown bile, the so-called B bile, as in the normal. There may occur a very faint increase in the intensity of the color, but it rarely becomes more viscous or turns to a deep brown. Microscopic examination made in six cases revealed, in each instance, the presence of pus cells, often in large clumps. This indicates the infectious character of the process.

Urobilogen was found in increased amounts in every case at the beginning of the disease and toward the end. During the height of the disease, it may be scanty or entirely absent, the duration of its absence depending on the severity of the disease. In the more severe cases it may disappear for a few days at a time, and is due to the fact that very little bile enters the duodenum at that period.

If the patient is seen during the earlier stages of jaundice, the amount of urobilogen may be found anywhere up to a 1:80 or 1:100 dilution. This soon diminishes to small traces, or may become absent altogether for short periods. After the disease has lasted for several weeks, the urobilogen again makes its appearance in large amounts, and soon rises to high figures anywhere up to a 1:250 dilution. The amounts vary daily. This stage may last as long as several weeks, presenting daily and often hourly variations. Its total disappearance indicates a restora-

tion of the liver function, even though a slight jaundice may still persist in the sclera or skin. The examination of the bilirubin in the serum at this stage also shows a return to normal. The slight staining of the tissues merely indicates an impregnation of the organs with bile pigment, which is very slowly given up.

The presence of urobilogen, even in traces, during the state of jaundice promptly rules out an obstruction or mechanical icterus, such as occurs in carcinoma of the head of the pancreas or of the biliary tract. This fact can be utilized to great advantage in the differential diagnosis between the jaundice due to hepatic causes and that due to extraneous mechanical causes. During the height of the disease, when urobilogen is absent from the urine, it may be somewhat difficult to differentiate between these two conditions. Repeated urine examinations, however,

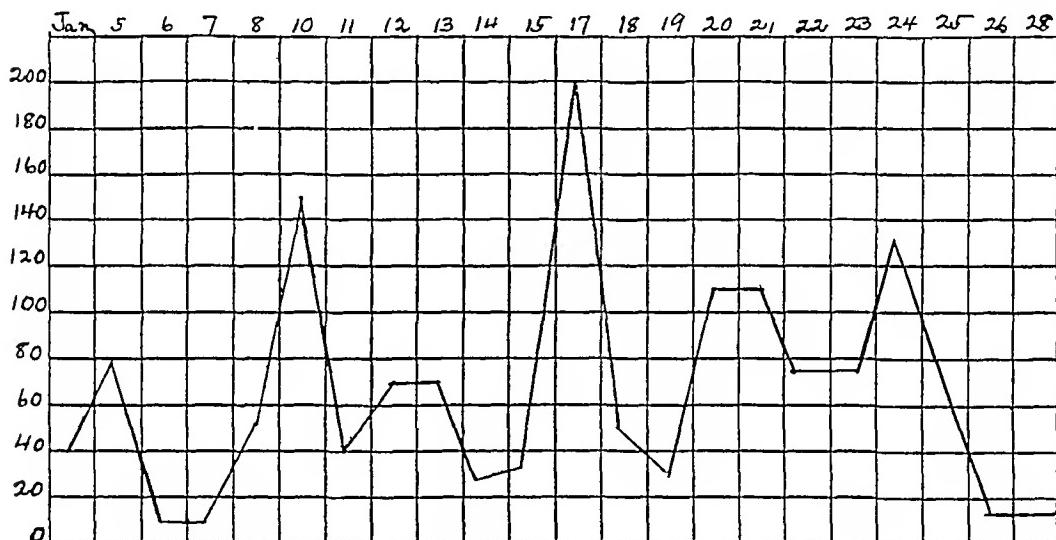


Chart 5—Daily output of urobilogen during course of a case of catarrhal jaundice.

will invariably aid in the diagnosis. In the catarrhal jaundice, it will reappear within a few days. Its continued absence for a week or longer speaks for a mechanical jaundice due to malignant causes. A point which may be of considerable significance is the fact that in the mechanical jaundice, if Ehrlich's aldehyd reagent is added to the urine, it changes within a few minutes to an intense green. This reaction we have always noted when the obstruction is extreme. We have always found it in the series of our dogs with ligation and excision of the common duct.

Septic Cholangitis with Liver Abscess—Two cases are here reported, one following in the wake of an apparently simple catarrhal jaundice, the symptoms of cholangitis coming on a few weeks after the patient had seemingly recovered from the disease. The patient suddenly developed an elevation of temperature with chills, the temperature

showing at times variations of ten degrees, between 97 and 107. Several weeks later, multiple abscesses were found on operation. The urobilogen was constantly present up to 1 200.

Another patient presented a history of digestive disturbances for some time prior to admission to the hospital. The patient ran similar high temperatures between 100 and 107 degrees, accompanied by severe daily chills and sweats. The urobilogen ran up to 1 500. After an illness of two months' duration, death occurred and the necropsy revealed multiple large and small abscesses in the liver.

Urobilogen in Chronic Liver Affections.—In chronic diseases, contrary to the acute states, one does not find an increase in the urobilogen as a constant factor. Many of the cases of hepatic cirrhosis here reported, with or without enlargement of the liver, with splenic enlargement and often ascites, failed to show pathologic increase in urobilogen. It has already been pointed out that a large factor of safety is presented by the liver regarding its functions, and how differently these diversified functions may be affected in disease. Only in grave pathologic conditions, such as acute yellow atrophy or phosphorus poisoning, may these functions be simultaneously involved.

That the liver is resistant to damage and can still perform its nitrogenous metabolism in spite of the fact that severe histologic changes can be demonstrated, has been shown by Howland and Richards,⁴¹ who, in a study of the metabolism in dogs following severe and delayed chloroform poisoning, have found no interference with this function. McMaster and Rous⁹ also have shown that, in the dog, nineteen-twentieths of the liver substance can be placed in a condition of stasis without the occurrence of tissue icterus. They find that such obstruction invariably results in atrophy of the affected tissue with compensatory hypertrophy elsewhere.

Our own observations point to the fact that the degree of interference with the liver function is dependent on the extent and rapidity of the disease process. In the slowly progressive liver affection, there appears to occur a gradual adaptation of the liver substance to carry on its function. The compensatory replacement of new cellular tissue is a well known characteristic of this organ. The occurrence of a large or fatty liver does not necessarily indicate a deficiency in its function. Neither does a chronically diseased liver with positive histologic changes always indicate a lack in the performance of its metabolic functions. Following are some of the findings in a series of chronic liver cases taken from the third medical division of Bellevue Hospital.

CASE 1.—Cirrhosis of the liver, large spleen, marked anemia, ascites, hematemesis, no jaundice. Urobilogen, 1 10. February 4, blood transfusion.

41. Howland and Richards. Metabolism and Pathology of Late Chloroform Poisoning, J. Exper. Med., 11, 344, 1909.

February 5, urobilogen rose to 1 60 February 7 and 8, urobilogen came down to the previous low figures of 1 10, the increase in urobilogen being due to destroyed red blood cells from the transfused blood

CASE 2—Banti's disease Urobilogen, variation from 1 10 to 1 100

CASE 3—Cirrhosis of the liver, marked anemia, ascites, jaundice of three months' standing Urobilogen, 1 20

CASE 4—Syphilitic liver Urobilogen, 1 30

CASE 5—Cirrhosis of the liver, jaundice, ascites, edema Tapped, 5 liters removed Urobilogen, 1 50, rose to 1 300 with increase in jaundice Necropsy report was hypertrophic cirrhosis, spleen moderately enlarged

CASE 6—Splenomegaly with anemia Urobilogen, 1 30

There were three cases of Hodgkin's disease Urobilogen, normal

In subacute conditions associated with various degrees of jaundice, the urobilogen is usually increased These appear to follow attacks of catarrhal jaundice and finally lead to a hypertrophic or Hanot cirrhosis They are characterized by persistence of jaundice lasting for months after the attack, accompanied by enlarged liver and spleen With exacerbations in the course of the disease, the amount of urobilogen may rise to high figures Two such cases have been under observation during the last year Both patients were young adults about 30, non-alcoholic, with negative Wassemann reactions In both, the disease had apparently developed in the wake of an attack of catarrhal jaundice The urobilogen varied ordinarily between 1 30 and 1 40 During an exacerbation which took place in one of the patients, there occurred an aggravation of the symptoms, the jaundice became more intense, the liver somewhat tender, and the gastro-intestinal disturbances more acute This condition lasted one month, during which time the urobilogen rose to 350, varying between 150 and 350, at the end of which period the jaundice gradually diminished to a slight icteric tint, the symptoms improved and the urobilogen came down to its previous level

Urobilogen in Cholecystitis and Cholelithiasis—In chronic cholecystitis and cholelithiasis, the urobilogen test showed no alteration in liver function in the majority of instances Out of a series of 150 cases, nineteen showed a slight rise in the urobilogen output, varying from 1 35 to 1 50 The remainder gave normal readings during repeated examinations In some of these cases, the bilirubin in the blood also was estimated, according to the Van den Bergh⁴² method The findings were likewise normal, the figure varying from 1 200,000 to 1 400,000

Four cases of chronic hydrops of the gallbladder, with large tumor masses, gave normal urobilogen and bilirubin figures

One case of acute cholecystitis and cholelithiasis with an elevation of temperature to 102 degrees and with severe colic requiring morphin, with

development of slight jaundice, probably indicating the passage of a stone through the common duct, gave a rise of urobilogen to 1 100, and bilirubin, 1 48,000

In one case of chronic cholelithiasis associated with diabetes with a large liver, the patient showing a subicteric tint, the urobilogen was 1 50 and the bilirubin 1 110,000. Here the abnormal rise could be attributed to the chronic hepatic disease.

The foregoing findings therefore tend to indicate that in the chronic stage of biliary diseases, neither the urobilogen in the urine nor the bilirubin in the serum show any deviation from the normal in the majority of instances, and give us little or no aid in the diagnosis of these conditions. They are significant only in acute stages.

Recently, attention has been called by Heyd⁴³ and others to chronic histologic changes in the liver occurring in association with chronic gall-bladder disease. Histologically, they were able to show these changes by removing small sections of the liver during the course of operation. The report of their findings, in the chronic lesions, indicated structural liver changes simulating both the atrophic and hypertrophic cirrhoses. Heyd claimed that fatalities following operations on the biliary tract were due to unexplainable toxemias resulting from chronic liver degeneration. The study of the foregoing cases, however, does not seem to bear out the existence of a chronic liver derangement with any such disturbance in its metabolic function.

Effect of Arsphenamin Therapy on Urobilogen Elimination.—Fifty cases of syphilis from the Bellevue College Clinic were examined during the course of arsphenamin therapy. Most of these were old cases having received several courses of antisyphilitic treatment. Only two cases were in the secondary stage with the presence of roseola. Urinary examinations were made prior to the administration of arsphenamin, and were followed up for two successive days after its injection. Thirty cases received neo-arsphenamin and twenty cases the old arsphenamin. It was found, on the whole, that the administration of arsphenamin had no effect on the increase of urobilogen. Only those cases which had somewhat high figures before the administration of arsphenamin gave slightly higher values after its administration. Thirty-nine cases had normal urobilogen figures, and these were not changed after the arsphenamin. In eleven out of the fifty, urobilogen readings before the injections were from 1 30 to 1 50. Three gave 1 30, two 1 40, three 1 50, one 1 75 and two 1 150. In one of the cases with secondary roseola in which the urobilogen was up to 1 150 before the administra-

⁴³ Heyd, C. G. The Liver and Its Relation to Chronic Abdominal Infections, Ann. Surg. 79: 55 (Jan.) 1924.

tion of arsphenamin, the urobilogen rose to 1 500 the day following its administration, however, it came down to normal within the next few days Two cases with 1 30 urobilogen came up after the old arsphenamin, one to 1 75, and one to 1 100 One case of 1 50 rose to 1 125 after old arsphenamin The remainder of those that gave originally higher readings remained unchanged

In this connection, some experiments also were made with intravenous injections of neo-arsphenamin in the dog An injection of 0 45 gm of this drug produced a rise in urobilogen of 1 30 the following day, which fell to normal on the third day A week later, the injection of 0 9 gm of neo-arsphenamin produced no rise The effects of the drug, therefore, on a normal liver appear to be very slight or absent altogether

Comparisons Between the Phenoltetrachlorphthalein and Urobilogen Tests in Various Liver Diseases—Six cases were selected for comparative study of the phenoltetrachlorphthalein and urobilogen output They comprised three cases of catarrhal jaundice, one case of splenomegaly with anemia, one case of syphilis with a large liver, and one case of marked cardiac decompensation with large liver and intense jaundice

Two cases of catarrhal jaundice gave negative reactions to the phenoltetrachlorphthalein test at the end of one hour The urobilogen tests on the same day were 1 60 and 1 70, respectively The first patient experienced a chill followed, for the next three days, by an increase in the output of urobilogen up to 1 200 The third patient with catarrhal jaundice developed a severe pain in the hepatic region promptly following the injection of the dye He also developed a phlebitis No reading was taken on this patient

The case with the cardiac decompensation, which gave constant high urobilogen readings varying from 1 300 to 1 1,500 gave less than a 1 per cent phenoltetrachlorphthalein reading

The splenomegaly case with anemia gave low urobilogen readings up to 1 40, and the phenoltetrachlorphthalein was 15 per cent

The case of syphilis gave persistently low urobilogen readings, whereas the phenoltetrachlorphthalein was 12 per cent

In the foregoing, we note differences in the behavior of the liver to phenoltetrachlorphthalein and urobilogen The retention of the dye does not necessarily indicate a deficiency in the performance of the normal metabolic function, but merely points to a lessened capacity of the liver to eliminate foreign substances It has already been pointed out that, in chronic liver diseases without parenchymatous changes, there occurs a gradual compensation of the liver to perform its normal

metabolic functions. When, however, foreign substances are suddenly thrown into the liver substances to which the liver is not accustomed, then the cell fails, and its eliminative power is retarded.

That the phenoltetrachlorphthalein is not entirely an innocuous substance can be seen from the cases herein reported, in which, in one instance, a severe pain in the hepatic region followed the injection and also a marked increase in the urobilogen output lasting a number of days. The complication of phlebitis has also been reported by others.

TABLE 3.—*Urobilogen Estimations in Urine in Certain Conditions*

Clinical Diagnosis	Number of Cases	Urobilogen	Bilirubin in Serum
Catarrhal jaundice	17	1.75 to 1.250	1.95,000 1.67,000 1.37,000 1.15,000 1.10,000
Cholangitis	1	1.500	
Cholangitis followed by liver abscess	1	1.200	1.35,000
Chronic cholelithiasis with diabetes subiective	1	1.50	1.110,000
Primary carcinoma of liver (necropsy)	1	1.350	1.203,000
Carcinoma of stomach with liver metastasis	2	1.150 to 1.300	
Carcinoma of head of pancreas	4	Absent	1.10,000 1.5,000
Carcinoma of stomach	8	Normal	
Carcinoma of esophagus	3	Normal	
Carcinoma of ovary and peritoneum	2	Normal	
Carcinoma of rectum	2	Normal	
Carcinoma of colon	1	Normal	
Carcinoma of lung	2	Normal	
Enlarged liver associated with chronic endocarditis	10	1.30 to 1.150	1.200,000
Marked cardiac decompensation associated with in tense jaundice (death)	1	1.1,500	
Gastric ulcers	7	2, 1.50, 5, normal	
Diabetes, during stage of acidosis	8	1.50 to 1.150	
Cholelithiasis and cholecvstitis	150	10, 1.35 to 1.50, 1. acute 1.100, the rest were normal	1.45,000 seven cases ex- cluded v. tried from 1.400,000 to 1.20,000
Chronic appendicitis	65	4, 1.35, 61 normal	1.400,000 to 1.200,000
Hydrops of the gallbladder	4	Normal	1.700,000 to 1.250,000
Tuberculous meningitis	1	1.80	

In Table 3 are given the urobilogen estimations in the urine in some of the conditions studied.

The remainder, comprising a series of close to a thousand cases of miscellaneous conditions, such as visceroptosis, nutritional disturbances, chronic infections of the tonsils and teeth, sinusitis, rheumatism, articular involvement, lumbago, psychoneurosis and bronchitis, all gave normal findings.

(2) HEMOLYTIC DISEASES

Pernicious Anemia.—Five cases are here reported, three in the active stage, and two in the terminal or aplastic stage. The first three presented high urobilogen outputs of 1.80, 1.75 and 1.50, respectively. The other two gave low urobilogen readings of 1.20 and 1.10.

The presence of an increased urobilogen in the anemias differentiates the primary from the secondary form. In the former, the excess

urobilogen is derived from the increase in the red blood cell production and destruction which is continuously going on, while, in the latter, there is no increase in the production of the red cells, but a conservation in their destruction, with the result of very low urobilogen elimination, often less than 1 10

The increase of urobilogen in pernicious anemia associated with an icteric tint of the sclera and skin and often a palpable liver presents difficulty at times in the differentiation between hepatic disease and primary anemia. Aside from the study of the morphology of the blood,

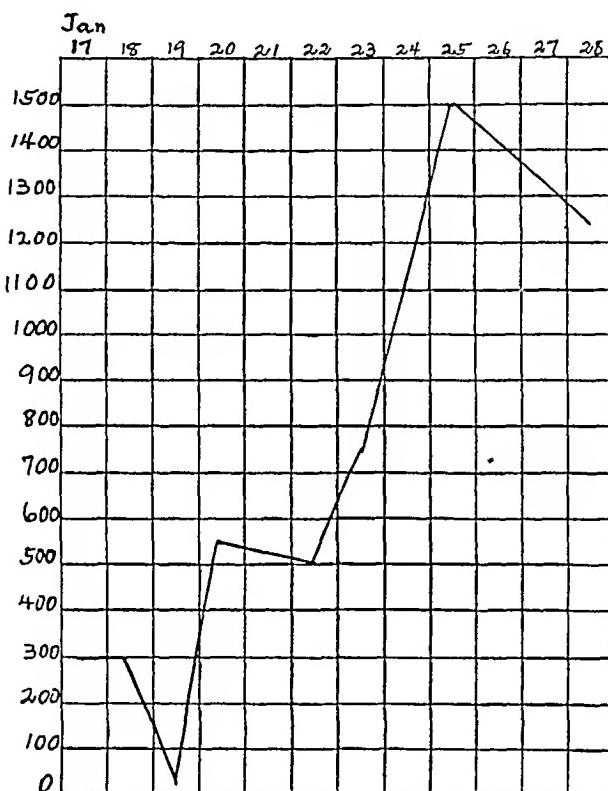


Chart 5.—Urobilogen elimination in case in which there was marked cardiac decompensation, large liver and intense icterus

the examination of the feces indicates an increased pigmentation to a dark brown color, in counterdistinction to the light or acholic feces accompanying liver disease. In the anemias, bile is never found in the urine, while in hepatic diseases associated with icterus, bile is always present.

Malaria.—The increase of urobilogen in malaria is a constant finding. This forms an important factor in the differential diagnosis between malaria and other infectious diseases. The diagnosis of malaria can often be made before the discovery of the parasites in the blood. A routine examination of the urine should always be made in infectious diseases with prolonged high temperatures.

Three cases of tertian malaria from the wards of Bellevue Hospital are here reported. One had the first attack in August, 1923. He came under observation in the hospital, December 11, with a blood count of 2,000,000 red cells, 50 per cent hemoglobin, and urobilogen, 1.50. December 14, the patient had paroxysms at 11 a.m., with urobilogen 1.75, and at 4 p.m., 1.100. Quinin administration was begun at 4 p.m. The following day, at noon, the urobilogen fell to 1.20, and remained normal after the quinin therapy.

Two other cases of malaria showed, on the day of the paroxysm, 1.300 urobilogen in one, and 1.150 in the other. Both of these cases presented difficulties in the clinical diagnosis. The discovery of a high urobilogen, with febrile paroxysms helped in the diagnosis of malaria prior to the finding of the parasites. The administration of quinin promptly reduced the urobilogen to normal.

SUMMARY AND CONCLUSIONS

1 A simple quantitative method for urobilogen estimation is described based on the Ehrlich's aldehyd reaction, and consisting of a series of dilutions which are made until no further reaction takes place. It has been found six times as sensitive as the spectroscopic method of Wilbur and Addis.

2 A series of animal experiments are here reported which were undertaken with the objects (1) to prove the relation between liver damage and increase of urobilogen in the urine and (2) to study the rôle of the intestine in the formation of urobilogen.

The results of these experiments indicate (a) that, in parenchymatous changes of the liver, such as induced by chloroform, there occurs a marked increase in the urinary urobilogen, (b) that urobilogen is formed normally in the intestinal canal by a process of decomposition of the bile pigment. In exclusion of bile from the intestinal canal by ligation and excision of the common duct, no urobilogen appears in the urine, even though the liver has undergone marked parenchymatous changes by subsequent chloroform administration. When, however, the flow of bile is reestablished by anastomosis between the gallbladder and duodenum, or when bile is administered by mouth, urobilogen again makes its appearance.

Only in rare instances of intrahepatic infections, as in cholangitis, may the urobilogen be formed within the biliary radicles. The presence of urobilogen in the liver bile is thus explained by intrahepatic infections and also by excessive amounts of urobilogen being brought to the liver from the intestinal canal.

The finding of small quantities of urobilogen in the intestinal canal in common duct occlusion is due to the excretion of bilirubin from the

general circulation into the intestines and its being there changed to urobilogen

3 The clinical significance of urobilogen has been studied in a series of over 1,200 cases, comprising catarrhal icterus, cholangitis, hepatic cirrhosis, cholecystitis and cholelithiasis, carcinomas of abdominal organs, cardiac decompensation, diseases of the hemopoietic system, granulomas, infectious diseases, malaria, and also a group of miscellaneous conditions, such as gastro-intestinal and nutritional disturbances and chronic infections, and including a large series of normal persons

We find that in the normal urine the urobilogen seldom rises above a 1:20 dilution. In constipation with putrefactive changes, it may become increased somewhat temporarily.

All pathologic conditions in which urobilogen is eliminated in excessive amounts can be classified into two main groups (1) diseases of the liver and biliary tract, and (2) hemolytic diseases.

In the former, it is associated with parenchymatous changes in the liver, causing an absolute insufficiency in the mobilization of urobilogen, while, in the latter, the increase of urobilogen is due to an increase in the bile pigment formation which produces a relative insufficiency of the liver. Both conditions may at times occur simultaneously, and, in fact, it seems quite probable that some liver damage also is present in hemolytic diseases.

Urobilogen is found in largest amounts in the acute and subacute liver changes and in exacerbations in the course of chronic processes. In the slowly progressive chronic liver lesion, the output of large amounts of urobilogen is not constant. This is probably due to the ability of the organ to perform its normal metabolic function by compensatory growth of new liver tissue.

In comparing the phenoltetrachlorophthalein to the urobilogen test in various liver affections, the different results may be explained by the difference in behavior of the liver cell toward foreign substances. Their retention does not always signify an insufficient metabolic liver function.

4 The constant presence of urobilogen in catarrhal jaundice, and its total absence in mechanical icterus, such as encountered in carcinoma of the head of the pancreas and of the biliary tract, forms a marked distinguishing diagnostic feature between this benign form of jaundice and those due to malignant causes.

5 Finally, we wish to advocate the use of the urobilogen test as a routine laboratory measure in all urine examinations. In icterus or latent icterus, in hepatic disorders, in the anemias, in malaria, in infections, in malignancies and in intoxications, it will supply an important adjuvant in the routine diagnosis, and will often aid in clearing up intricate and obscure clinical conditions.

BLOOD VOLUME

IV DIURNAL FLUCTUATIONS IN BLOOD VOLUME AND CHANGE INCIDENT TO TRANSFUSION REACTION *

WINIFRED ASHBY, PH D

ROCHESTER, MINN

Diurnal fluctuations in the count of corpuscles derived from a transfusion appear to have a consistent trend in patients with anemia, and are assumed to indicate blood volume changes. Changes incident to transfusion, pointing to a reduced blood volume following a transfusion reaction, have also been noted.

Little attention has been given to rapid fluctuations in the blood count, and the possibility of their occurrence is often lost sight of. Limbeck¹ studied the changes in the red and white cell count after eating, and reports a drop in the red cell count. He found a count of 5,550,000 before the meal, 5,320,000 a quarter of an hour after the meal, 5,480,000 an hour and a quarter after, 4,730,000 two hours and a quarter after, 4,870,000 three and a quarter hours after, and 4,720,000 four hours and a quarter after. In reviewing the literature, he found that Sorenson noted an increase in the red cells of from 15 to 19 per cent about an hour after food was taken, while Reinhardt, Vierdt and Duperl found a diminution. Dreyer² has recently studied the question of diurnal changes in the hemoglobin, making observations at short intervals throughout the twenty-four hours by means of a technic which he considers accurate to within a few per cent. He gives five representative curves. In one of these there is a definitely progressive drop in the hemoglobin percentage from 10 a m to 4 p m, with a subsequent rise, reaching its peak at 4 a m. In the other curves are marked irregularities that seem to have no definite trend. Dreyer considers that the fluctuations are irregular, but that the late afternoon is a time at which the hemoglobin percentage readings are more stable, and that the greater fluctuations occur in patients with anemia. Dreyer obtained the blood for the determinations from a freely dripping puncture. Rabinovitch³ more recently studied the variation of the hemoglobin percentage in twenty normal subjects, taking readings every two hours from 8 a m to 6 p m.

* From the Mayo Foundation

¹ Limbeck, R R. The Clinical Pathology of the Blood, London, New Sydenham Society, 1901, p 184

² Dreyer, G, Bazett, H C, and Pierce, H F. Diurnal Variations in the Hemoglobin Content of the Blood, Lancet **2** 588-591 (Sept 18) 1920

³ Rabinovitch, I M. Variations of the Percentage of Hemoglobin in Man During the Day, J Lab & Clin Med **9** 120-123 (Nov) 1923

He noted maximal variations ranging from 11 to 26.2 per cent with no definite trend to the variations. It is perhaps a matter of coincidence, but, as his figures are given, it happens that in the four subjects showing the greatest maximal variation, 20.2, 21.4, 26 and 26.2 per cent, the low percentages occur in the afternoon.

It would seem more probable that these changes in the hemoglobin were either due to redistribution of the corpuscles, or to changes in plasma volume, and not to destruction and production of corpuscles. The latter possibility I have, in part at least, ruled out by testing the fluctuations in the counts of the transfused corpuscles, and finding that they, too, show fluctuations which tend to parallel those found in the native red blood count, the discrepancies between the two sets of readings being inconsiderable, in view of the degree of accuracy of the technic, although it is conceivable that there might be some significance to them.

My interest in diurnal fluctuations in the cell count as a probable indication of blood volume change was enlisted by the marked differences that were often noted between counts taken at different times of the day in patients with pernicious anemia, who were at the beginning of a course of treatment. As the patient improved, there was a tendency for the counts to become less irregular. One case (Case 80) especially was studied from this point of view. Counts were taken between 8 and 9 a.m., and in the evening. The study was begun immediately after the first transfusion. The fluctuations of the count of unagglutinable corpuscles indicated at first volumes which changed from 72 to 47 cc for each kilogram of body weight, the higher volume being found in the morning. In the course of nine days, as the patient's condition improved with rest in bed and forced fluids, the volume, as determined by the count of unagglutinable corpuscles, gradually increased to 83 cc for each kilogram of body weight, and the fluctuations became negligible. This increase was not accompanied by any marked improvement in the number of native corpuscles found in each cubic millimeter of blood, although if the interpretation of the decrease in the number of unagglutinable corpuscles, as indicating a blood volume increase, is correct, the total number of corpuscles in the circulation was considerably augmented. As compared with the fluctuations reported for normal subjects by Rabinovitch, and for normal and anemic subjects by Dreyer, the fluctuations, in this subject, were greater at the beginning of treatment, and less after improvement had taken place.

Studies were made of blood volume changes through the day. It was not practicable to make many determinations in one day, but four consecutive studies were made on a patient with pernicious anemia, who was in bed in the hospital, the count remained low throughout the study.

Two studies were made on a patient with pernicious anemia, who was out of the hospital and in better condition, and two more intensive studies were made on a patient with purpura, who was fairly well. Also a small

TABLE 1—*Durnal Variation in Blood Red Cell Count Unagglutinable Corpuscles*

Case	Date	Time	Red Cell Count		Unagglutinable Corpuscles		Diagnosis and Remarks
			In Millions	Per Cent Change	In Millions	Per Cent Change	
151	3/10/21	Transfusion with unlike group blood					
	3/11/21	9 00 a m	2 12	0	0 760	0	Pernicious anemia
		4 15 p m	1 53	-28	0 638	-16	
	3/14/21	9 15 a m	1 61	0	0 578	0	
		3 00 p m	1 39	-15	0 529	-8	
		5 00 p m	1 28	-5	0 556	-4	
	3/16/21	9 00 a m	1 88	0	0 701	0	From ear
		9 00 a m	1 61	0	0 649	0	From vein
		12 00 m	1 59	-15	0 657	-6	From ear
		3 30 p m	1 57	-15	0 583	-17	From ear
		3 30 p m	1 10	-23	0 498	-22	From vein
		7 00 p m	1 75	-13	0 680	-3	From ear
	3/17/21	Transfusion					
	3/24/21	9 10 a m	1 94	0	0 594	0	
		11 30 a m	1 94	0	0 573	-4	
		3 20 p m	2 07	+6	0 524	-12	
		9 30 a m	1 91	-1	0 602	+1	
97	9/3/20	10 00 a m	2 70	0	0 534	0	From ear Pernicious anemia
		2 30 p m	2 63	-5	0 641	+20	From vein
		9 00 a m	2 09	-23	0 583	+10	From vein
	9/10/20	9 20 a m	2 82	0	0 513	-4	From ear
		3 00 p m	2 45	-13	0 584	+10	From vein
		8 15 a m	2 47	-12	0 633	0	From ear
					0 622	0	From vein
					0 657	-4	From ear
					0 513	-16	From vein
					0 590	-14	From ear
					0 576	-7	From vein
116	2/6/20	7 45 a m			0 490	-4	In bed Purpura
		9 45 a m			0 502	-2	In bed
		11 00 a m			0 511	0	Up and about
		11 30 a m			0 512	0	
		1 15 p m	5 91				
		1 30 p m			0 490	-4	
		3 00 p m			0 446	-13	
		5 30 p m					
		6 00 p m			0 466	-9	
		6 40 p m	5 14		0 553	+8	
		9 50 p m			0 520	+2	
	2/11/24	12 40 a m	5 33		0 423	-13	
		8 25 a m	5 04	-7			
		10 15 a m			0 488	0	
		10 55 a m	5 42	0	0 486	0	
		11 20 a m			0 487	0	
		11 40 a m	5 25	-4	0 470	-4	
		12 10 p m			0 453	-7	
		1 15 p m	Luncheon				
		1 30 p m	5 00	-8	0 435	-11	
		2 55 p m			0 438	-10	
		3 55 p m			0 442	-9	
		5 15 p m	5 17		0 453	-7	
		6 45 p m	Dinner				
		7 30 p m	5 38		0 500	+12	
		9 00 p m	Hot lemonade				
		9 15 p m			0 413	-13	
		11 15 p m			0 430	-12	
		12 50 p m			0 438	-10	
80	8/31/19	10 00 a m	1 93	0	0 522	0	Pernicious anemia
		3 00 p m	1 99	+3	0 545	+4	
		6 00 p m	2 06	+6	0 564	+8	

study on a patient previously mentioned (Case 80) is included because it proved an exception to the trend in the change of count. In some instances, counts were made both on blood from the ear and on blood

from venipuncture. The percentage of change is based on the first count obtained after breakfast. Duplicate or triplicate counts were made in all instances, and only those which gave satisfactory checks are included in Table 1.

In the case of the patient with pernicious anemia who was in bed in the hospital, and who was tested four times, there was a lower count, indicating a greater blood volume in the afternoon than in the morning.

TABLE 2.—*Variation in Blood Volume as Indicated by Variations in the Cell Count Following Transfusion*

Case	Time After Transfusion	Red Cell Count in Millions	Unagglutin- able Cor- puscles in Millions		Blood Volume	Temper- ature	Remarks
			Unagglutin- able Corpus- cles in Millions	Blood Volume			
97	Before		1.90	0.070			
	10 minutes	1.89	0.496	5,350			
	35 minutes	2.20	0.498	5,350			
	30 minutes		0.543	4,800			Severe shivering
	42 minutes		0.566	4,600			Severe shivering
	70 minutes	1.78	0.495	5,350	102.2		
	4 hours	2.24			102.4		
94	18 hours	2.19	0.403	6,100			
	Before		2.03	0.440	4,900	98.7	Patient in Group 4 received a Group 4 transfusion following a Group 2 transfusion. Unagglutinated corpuscles are Group 2 corpuscles
	40 minutes	2.63	0.589	3,700			
	3 hours	2.58	0.553	3,900			
	18 hours	2.25	0.448	4,700			Slight chill
212	Before		1.16	0.031			
	10 minutes	1.10	0.046	3,820			
	40 minutes	1.61	0.724	3,400			
	18 hours	1.64	0.737	3,340	102	99.2	Vomited
207	Before		1.75				
	10 minutes	2.14					
	40 minutes	2.08					
	70 minutes	2.13					
	18 hours	2.07					Lymphatic leukemia, high count of white cells, no transfusion reaction
116	Before		4.58				
	10 minutes	4.79	0.556				
	40 minutes	4.82	0.566				
	18 hours	4.96					No transfusion reaction
29	Before		2.06	0.128			
	After		2.56	0.637	3,400		Group 1 transfusion
	18 hours	3.06	0.760				
	2 days	2.23	0.548	4,600			Chill day after transfusion

on evening. The counts on the patient with purpura, who was ambulatory, indicated that the blood volume was high while he was in bed in the morning, became less after he had been up and had had his breakfast, increased further in the afternoon, and decreased after dinner on both days that the tests were run, although on one day, when hot lemonade was taken at 9 in the evening, there was an increase in volume which was still evident at midnight. In the case of the patient with pernicious anemia, who was in the better condition, there was an increase in the blood volume in the afternoon on one day, but on the occasion of the other test, there were irregularities in the results for which I cannot

account These data would, on the whole, indicate that there is a tendency for the blood volume to increase in the afternoon in some persons who are not normal On the other hand, in six comparisons between the morning and afternoon counts which were made on a normal subject, no definite tendency appeared The maximal percentage of variation was considerably less

Of interest in this connection is some work reported by Price-Jones⁴ on the diurnal variation in the size of the red corpuscles He finds considerable variation due to changes in the hydrogen ion concentration of the blood In the morning before any exercise has been taken, he finds the corpuscles smallest They increase in size during the day and fall again after midnight The investigation was made on his own blood Of the three curves that were made, one was representative of a study of the changes which occurred while the subject remained in bed for twenty-four hours In this curve, although the general shape is the same as that of the other two taken during a normal day's activity, there is a marked fall in the size of the average diameter of the corpuscles between 3 and 6 p m , during which time two observations were made Although the author does not stress this point, it is of interest in view of the change in blood volume found in patients during this time, as the results obtained from the subject kept in a state of comparative inactivity would be likely to be more comparable to those obtained from a patient whose activity is reduced

Changes in weight in tuberculous patients, reported by Scott,⁵ are also of interest in this connection The patients were weighed at 10 a m , and between 2 and 4 p m Of 962 patients, 611 weighed more in the afternoon than in the morning, the difference being from 0.25 to 4 pounds In the positive cases, there was a greater difference between the morning and afternoon weights than in the suspects, and the more advanced the disease, the greater the difference As the patients who were in the worse condition had the greatest increase in weight in the afternoon, the figures would suggest that there was some factor other than the increase in weight of the intestinal contents resulting from the intake of food, and that the body tissues themselves, of which the blood may have been the most important, increased their water content

Changes in hydrogen ion concentration of the blood immediately suggest themselves as the cause of the changes in blood volume, but no parallel studies of hydrogen ion concentration of the blood were made Changes in hydrogen ion concentration would be expected to affect the

4 Price-Jones, C The Diurnal Variation in the Sizes of Red Blood Cells, *J Path & Bacteriol* **23** 351-383 (Dec) 1920

5 Scott J M Diurnal Variation in Body Weight in Tuberculous Patients, *Lancet* **2** 639-640, 1919

plasma volume and the total corpuscle volume in opposite directions. We know that an increase in hydrogen ion concentration within the range of the hydrogen ion concentration of the blood causes a decrease in corpuscle volume. Although I have seen no work on the variation in osmotic pressure of blood serum with variation in hydrogen ion concentration, I think it safe to assume, in view of the work of Sorenson⁶ and Loeb⁷ on egg albumin and gelatin, that both the chief constituents of the blood serum increase in osmotic pressure with an increase in alkalinity within the range of the hydrogen ion concentration of the blood, although in view of the fact that their iso-electric points are different, the curves for their rate of change within the same range of hydrogen ion concentration may be quite unlike. The change in the whole blood volume would be due to the combined effect of the decrease in the size of the corpuscles and of the increase in osmotic pressure of the serum proteins. The sum of these changes, if this is the explanation, is apparently smallest in normal subjects in whom the corpuscle and plasma volumes are more nearly equal, and greater in anemic subjects in whom the corpuscle volume is diminished. On this basis, it would seem that the increase in the plasma volume usually approximately balances the decrease in corpuscle volume caused by decrease in hydrogen ion concentration of the blood in normal subjects, whereas in anemic subjects the corpuscle decrease in volume is not enough to balance the serum protein increase in osmotic pressure producing the more unstable blood volume. It would seem probable also that differences in the proportion of serum albumin and serum globulin may play a part. A study of the tendency to instability of blood volume in correlation with the protein composition of the blood would be of interest. The fact that this increase in blood volume in the afternoon has tended to appear in patients who are inactive, and not in the normal subject studied, may also be due to some physiologic alkaline tide, perhaps that of digestion, which in the normal subject was masked by bodily activity.

CHANGE OF VOLUME DURING TRANSFUSION REACTIONS

A few studies were made on patients following transfusion, both during a reaction and when there was no reaction. As the transfusions were given in the early afternoon, and reactions usually occur in one-half to one and one-half hours after transfusion, the time of day at which these transfusion reactions occurred was that at which normally there would tend to be an increase in blood volume. My few studies

⁶ Sorenson, S T Studies on Proteins, Compt rend Lab de Carlsberg, Copenhagen, 1917

⁷ Loeb, J Proteins and the Theory of Colloidal Behavior, Ed 1, New York, McGraw-Hill Book Company, 1922

would seem to indicate that whether or not there was an initial increase in blood volume following transfusion, over and above that produced by the transfusion itself, when a transfusion reaction occurred, it was accompanied by a decrease in volume. This decrease was not observed in cases in which no reaction resulted from transfusion. From the data given in Table 2, it will be seen that the magnitude of the decrease in volume is of about the same order as the greater increase in volume found in the more sensitive patients in the diurnal change at this time.

The counts from which these volume computations were derived were made on blood from an ear puncture, and may have been influenced by the admixture of blood from the capillaries, in which a greater tendency to congestion is possible on puncture during the transfusion reaction than before. As simultaneous venipuncture was not done, this possibility cannot be ruled out. I am, however, of the opinion that it is the less probable explanation of the increased count, and that this was more probably due to a decrease in blood volume. The greater instability of blood volume, which appears to exist in patients who are in the initial stages of their treatment, and the finding of Butsch and Ashby,⁸ that in a series of 265 transfusions, eighty-one patients with a hemoglobin below 30 per cent had a markedly greater tendency to reaction (45 per cent against 35 per cent), would make it seem probable that there may be some common ground for the tendency to instability of blood volume and the tendency to transfusion reaction, since these patients with the lower hemoglobin were on the whole those who were in the initial stages of their treatment.

⁸ Butsch, J. L., and Ashby, Winifred. The Effect of the Digestive Period and Other Factors in Reactions After Blood Transfusions, New York M J **113** 513-517 (April 6) 1921.

BLOOD VOLUME

V THE EFFECT OF TREATMENT ON THE BLOOD VOLUME OF PATIENTS WITH PERNICIOUS ANEMIA¹

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The blood volume of patients with pernicious anemia was calculated from the count of unagglutinable corpuscles during the course of a series of transfusions. The number of corpuscles for each cubic millimeter was counted, the total number of corpuscles present in the circulation computed, and an attempt was made to correlate the three factors, blood volume, red cell count and total number of corpuscles, with the general condition of the patient.

The studies were started simultaneously with the treatment of a patient who either had not been treated before, or who had come back for a course of treatment after a relapse. A transfusion of unagglutinable corpuscles was given first, followed by a series of transfusions of blood of the same group as that of the patient. These studies were made incidental to a study of the rate of elimination of transfused blood in patients with pernicious anemia. At the time when they were made, it was not feasible to confirm by other methods the changes in volume which apparently occurred, although, in some instances, it was possible to make a partial check by means of a second unlike group transfusion. A blood volume, however, determined from change in unagglutinable corpuscles before and after transfusion, is open to the possibility of error already considered,¹ but, as the number of corpuscles present before transfusion is not greater than the number added, the error which might be introduced by fluctuations in blood volume would be such that the result may be regarded as of value for verification. The results have also been checked to a certain degree by a comparison of the maximal blood volumes in this series with those in similar cases by other workers using the vital red method. The possibility that the apparent increase in the blood volume resulting in many instances from a series of transfusions might be due to destruction of the unagglutinable corpuscles initially transfused, rather than to their dilution, was still further investigated, in some cases, by giving the transfusion of unagglutinable blood from which the blood volume was derived as a later member in a series of transfusions. It was then possible to compare the

* From the Mayo Foundation

1 Ashby, Winifred Blood Volume III Apparent Changes in Blood Volume Indicated by Transfusion, and Their Bearing on Methods of Determining Blood Volume by Means of the Degree of Change in a Constituent of the Blood, Following Transfusion of a Known Amount of That Constituent, Arch Int Med 35 641 (May 15) 1925

blood volume so obtained with volumes indicated after a similar degree of treatment in cases in which the transfusion of unagglutinable blood was the initial transfusion

The patient's own impression of his condition, my impressions as I saw him in the course of the experiment, the hospital records, and the clinician's resume of the case, before and after treatment, were made use of in determining the change in condition due to treatment. As Lindeman² considered that there was a correlation between a high blood volume and the ability to endure a low cell count without so much inconvenience from "palpitation of the heart and ringing in the ears," the patients were questioned as to this point. Note was made of throbbing sensations in the body and ringing in the ears.

Of the numerous cases studied, the complete data on a few which seem to be representative are given, and also the data on one (Case 59), which seems to be exceptional. The patients may be classified as follows: (1) those whose blood volume and cell count were initially low, who were in very bad condition, and who improved without any considerable increase in cell count as determined by the cell content for each cubic centimeter of blood, but with a comparatively marked increase in blood volume and total cell count; (2) those who improved only little, and whose apparent blood volume and cell count remained low; (3) those who had a nearly normal blood volume, and were in fairly good condition before treatment, and who made a good recovery following transfusion; and (4) an occasional case in which the initial blood volume and count were low and in which there was an improvement in the cell count before there was an increase in blood volume.

REPORT OF CASES

CASE 70—A man, aged 62, had pernicious anemia. He was in very poor condition. On physical examination, a pulsating wave in the upper abdomen was noted (probably pulsating aorta), and a bruit over the femoral vessels. He improved markedly under treatment, and became able to take fairly long walks.

TABLE 1.—*Findings in Case 70*

Days of Treatment Transfusion of unlike group blood	Red Cell Count in Millions	Corpuscles to 1 cc. Kilogram of Body Weight	Cells for 1 cc. Kilogram of Body Weight
0	1.02	55×10^9	54
1	1.28	96×10^9	75
3	1.13	89×10^9	79
4	0.88	77×10^9	88
4 Transfusion			
5	1.11	108×10^9	97
8	1.40	131×10^9	94
11 Transfusion			
14	1.79	159×10^9	89
17	1.62	167×10^9	103
18	1.64	177×10^9	120

² Lindeman, E. The Total Blood Volume in Pernicious Anemia, J. A. M. A. 70: 1292-1297 (May 4) 1918.

CASE 43—A man, aged 49, had pernicious anemia. He was given the first series of transfusions and died three years later.

TABLE 2—*Findings in Case 43*

Days of Treatment	Red Cell Count in Millions	Corpuscles to Each Kilogram of Body Weight	Cc of Blood for Each Kilogram of Body Weight	Remarks
Transfusion of unlike group blood				
1	1.95	119×10^9	61	Ringing in the ears and throbbing
2	1.85	124×10^9	67	
4	1.71	152×10^9	89	Ringing and throbbing stopped
8 Transfusion				
11	2.20	104×10^9	88	
14	1.90	154×10^9	83	
14 Transfusion				
14	2.40	230×10^9	96	
36	2.40	258×10^9	108	
45	2.32	259×10^9	108	Patient feels much better
51			85	Patient weaker
53	2.16	181×10^9	84	Patient stronger
56	1.84	157×10^9	85	Patient stronger
59	Drop occurred in the count of transfused corpuscles indicating elimination, ringing in ears and throbbing commenced again			
60 Transfusion				
66	2.13			Ringing in ears stopped
66 Transfusion				
68	2.16			
91 Transfusion of unlike group blood				
91	2.39	201×10^9	84	

CASE 57—A man, aged 63, had pernicious anemia. The patient complained of ringing in his ears, and a throbbing sensation. He had noticed weakness for the last two years. On examination just before transfusion, a soft, booming systolic murmur and edema were noted. The patient received the first series of transfusions.

TABLE 3—*Findings in Case 57*

Days of Treatment	Red Cell Count in Millions	Corpuscles to Each Kilogram of Body Weight	Cc of Blood for Each Kilogram of Body Weight	Remarks
Transfusion of unlike group blood				
0	1.51	85×10^9	55	Ringing in ear and throbbing sensation
1			55	
2	1.55	79×10^9	51	Ringing in ear and throbbing sensation
4	1.31	66×10^9	50	Ringing in ear and throbbing sensation
6	1.65	89×10^9	54	Ringing in ear and throbbing sensation
7	1.72	88×10^9	51	Ringing in ear and throbbing sensation
9	1.89	104×10^9	55	Ringing in ear and throbbing sensation (felt better, gain in weight)
11	1.95	113×10^9	58	Ringing in ear and throbbing sensation
13	2.17	107×10^9	50	Ringing in ear and throbbing sensation
14	1.53	106×10^9	69	Less ringing and throbbing
14 Transfusion				
15	2.24	166×10^9	74	Ringing and throbbing ceased
20	1.84	127×10^9	69	
21 Teeth extracted				
23	1.87	122×10^9	65	Ringing in ears at night
27	1.87	127×10^9	68	

Two months later, the patient returned, complaining of ringing in the ears and throbbing in the abdomen. He received a like group transfusion, soon after which these symptoms disappeared. An unlike group transfusion, following this, gave the data for a blood volume estimate, which was 111 cc for each kilogram of body weight. At this time, the red cell count was 1,480,000, and the total cells for each kilogram of body weight was 164 by 10^9 . A

second Group 1 transfusion, seven days later, gave data for a volume estimate of 101 cc for each kilogram of body weight. After a fourth transfusion, in this series, the patient was dismissed. The clinician's summary was "appetite better, slight weight increase, not stronger, not much improvement."

CASE 54.—A man, aged 44, had pernicious anemia. The patient did not complain of ringing in the ears or throbbing. He received a series of three transfusions. He returned five months later in fair condition, and died seven months later.

TABLE 4—*Findings in Case 54*

Days of Treatment Transfusion	Red Cell Count in Millions	Corpuscles to Each Kilogram of Body Weight	cc of Blood for Each Kilogram of Body Weight
0			68
3	1.59	106×10^9	67
6	1.63	130×10^9	80
6 Transfusion			
7	1.84	157×10^9	85
11	2.17	145×10^9	67
12 Transfusion			
12	2.20	150×10^9	68
13	2.12	153×10^9	72
17	2.05	140×10^9	68

CASE 59.—An obese woman, aged 52, had pernicious anemia. She had had previous transfusions and a remission of symptoms. At the time of this study her blood count was 1,330,000. She was given an unlike group transfusion of 475 cc, after which she greatly improved, her health became practically normal, and remained so for about three years. She did not complain of throbbing sensations or ringing in the ears.

TABLE 5—*Findings in Case 59*

Days of Treatment	Red Cell Count in Millions	Corpuscles to Each Kilogram of Body Weight	cc of Blood for Each Kilogram of Body Weight	Remarks
Transfusion of unlike group blood				
0	1.88	92×10^9	49	
1	1.77	74×10^9	42	
7	1.52	71×10^9	47	
11	1.61	83×10^9	52	
22	2.98	90×10^9	31	Very hot weather, patient felt well
26	3.55	114×10^9	32	
28	3.47	115×10^9	33	
31		reserve		Began taking sodium bicarbonate, 8 gm required to make urine alkaline
33	3.97	306×10^9	77	
34			68	
			73	
38	4.02	840×10^9	82	
40	4.50	396×10^9	88	
43	4.79	392×10^9	82	
57	4.89	430×10^9	88	

CASE 97.—A man, aged 42, had pernicious anemia. He did not complain of ringing in the ears, or of throbbing sensations. He received his first series of transfusions, and became comparatively well. Later, a splenectomy was performed. He was in good health four years after this study.

TABLE 6.—*Findings in Case 97*

Days of Treatment	Red Cell Count in Millions	Corpuscles to Each Kilogram of Body Weight	Cc of Blood for Each Kilogram of Body Weight
Transfusion of unlike group blood			
0	1.89	142×10^9	75
1	2.19	211×10^9	96
6	2.12	242×10^9	114
10	2.12	193×10^9	91
11	2.86	266×10^9	93
13	2.87	250×10^9	87
15	2.75	256×10^9	94
17	2.42	245×10^9	101
17 Transfusion	2.55	222×10^9	87
28 Transfusion	3.36	316×10^9	94
31	3.03	240×10^9	79
42	2.87	244×10^9	85
49 Patient home in excellent condition	Ten months later, after a series of transfusions which were ineffective, a splenectomy was performed, followed three days later by a transfusion		
Transfusion			
25 Transfusion of unlike group blood			
26	2.70	175×10^9	65
31	2.60	162×10^9	62
78			80
78 Transfusion of unlike group blood	2.44	224×10^9	92

COMMENT

Case 70 is a striking example of Group 1. In a similar case, the increase in blood volume was verified by a second unlike group transfusion. Case 43 is a less striking illustration of the same group, in that the blood volume (61 cc for each kilogram of body weight) and blood count were not so low initially, and the patient was in better condition. In this case, after the almost complete elimination of the unlike group transfusion, a blood volume determination was made possible by a second unlike group transfusion following two like group transfusions. A blood volume of 84 cc for each kilogram of body weight was found, which was comparable to the blood volume that had apparently previously been established by a series of transfusions. This finding increases the probability that the improvement in blood volume which apparently occurred during the first series of transfusions was a reality, and not the result of an elimination of unlike group transfused corpuscles. Cases 57 and 54 illustrate Group 2. Case 97 illustrates Group 3. A series of transfusions rendered this patient's blood nearly normal for a time. A splenectomy, which was performed after a stubborn relapse, was followed by a poorer condition, the blood volume was lower and took longer to become normal. Case 59 is exceptional in that a single transfusion initiated a marked and prolonged remission. The woman was obese and her blood volume was initially low. It apparently reached the low figure of 31 cc for each kilogram of body weight during some very hot weather, without any inconvenience to the patient. However, as the patient's skin tended to be flushed, I am

inclined to suspect that the high count in the unagglutinable corpuscles which caused the calculation of a low blood volume may have been produced to some extent by congestion of corpuscles in the capillaries. Thirty-one days after the transfusion, coincident with the administration of small daily doses of sodium bicarbonate, there was a drop in the unagglutinable corpuscles. This, if due to increase in blood volume, indicates the establishment of a normal blood volume. The cell count, at this time, increased to 4,000,000. At this length of time after transfusion, however, a drop in the number of transfused cells is more safely regarded as their elimination.

The higher values obtained in this series are of the same order as those reported by Keith³ using the vital red method. They are usually in the vicinity of 85 cc for each kilogram of body weight, in a few instances, they are over 90, values of 103, 108 and 114 appear. One value of 120, which appeared at the end of the series in Case 70, may well have been due to destruction of transfused corpuscles, although it is not out of keeping with values reported by Keith in cases of leukemia. In a series of nineteen determinations reported by Keith on patients with pernicious anemia, nine had volumes ranging from 81 to 89, one had a volume of 92, one 102, and one 106 cc for each kilogram of body weight. Keith, unlike Bock⁴ finds much variation in plasma volume percentages among different patients, and also in individual patients. Although the results given here have not been calculated in terms of plasma volume, it is obvious that the increases indicated would, in most cases, have to be mainly in the plasma volume, as the corpuscle increase was usually not sufficient to account for the difference.

There were a few instances in which the unlike group transfusion, from which the blood volume determination could be made, was not the first transfusion. The immediate blood volume calculations obtained in these cases are parallel to the values indicated at the same length of time after the initial transfusion in cases in which the unagglutinable blood was given at the first transfusion, and had consequently been in the circulation for some little time when the determinations were made. This would still further support the validity of the apparent increases in blood volume on a series of transfusions seen in some cases. Besides Case 43, in which, when the unlike group transfusion was the third in the series instead of the first, a value of 84 was obtained, and Case 57,

³ Keith, N. M. The Total Circulating Volume of Blood and Plasma in Cases of Chronic Anemia and Leukemia, Am J M Sc **165** 174-184 (Feb) 1923

⁴ Bock, A. V. The Constancy of the Volume of the Blood Plasma, Arch Int Med **27** 83-101 (Jan) 1921

in which a second transfusion gave a value of 111, there are three other cases. In Case 60, in which a second transfusion gave a value of 63, in Case 49, in which a third transfusion gave a value of 91, which was slowly decreased during the succeeding eleven days, and in Case 112, in which the fifth transfusion in two months gave a blood volume value of 87 c.c. for each kilogram of body weight, this value was maintained. On the whole, these figures, obtained immediately from the later unlike group transfusions, are representative of a cross section of the foregoing studies and indicate that the apparent increase in blood volume, which occurred in certain cases, was probably not due to destruction of the transfused corpuscles, but to their dilution by blood volume increase.

SUMMARY

The patients who were in the worse condition at the beginning of their treatment had the lower blood volumes. The blood volumes of patients who were made much more comfortable by their transfusions increased, even, in some instances, without a great increase in the cell count for each cubic millimeter, although with the increase in plasma indicated, the total amount of circulating corpuscles was greatly increased. It seems probable that when a patient is not definitely gaining, so far as his hemoglobin is concerned, a decrease in the plasma volume means a fall in the cell count. I am inclined to think that, if a patient's blood destroying mechanism will tolerate an increase in the level of his cell count, an increase in the count with a stationary or even compensatory falling plasma volume may be of advantage, but that if his blood destroying mechanism is so sensitive that it will not tolerate much increase in the level of the blood count, then the increase in plasma volume, causing a total increase in the corpuscle content without greatly raising the level of the cell count, would be helpful. Except in the case of the obese woman, there seems to be a relationship between the throbbing sensations and ringing in the ears, and the low blood volume. Generally, these symptoms disappeared with the establishment of a blood volume of 57 c.c. for each kilogram of body weight.

THE MECHANISM OF REACTION OF NONSPECIFIC PROTEIN AGENTS IN THE TREATMENT OF DISEASE

II THE INFLUENCE OF VARIOUS AGENTS ON THE MOBILIZATION OF BLOOD ANTIBODIES^{*}

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When a suitable foreign protein is carefully administered to a patient suffering from acute or chronic infection, there is no doubt that the patient will give evidence of increased antibody production, measured by agglutinin titer, opsonic index, bacteriolytic activity and methods of complement deviation, as observed and repeatedly confirmed by different workers. Here, however, the clinical findings often fail to measure up to the laboratory expectations.

On the other hand, the possibility of these antibodies, as they are mobilized, playing an important rôle, at least in the ultimate recovery of the patient, cannot be ignored, though the temporary relief of the symptoms might not necessarily depend a great deal on them.

Theories have been advanced to explain the mechanism of serum antibody fluctuation, but the opinions of different observers vary as do the results obtained by them.

Teaque and McWilliams¹ show that the intravenous injection of a suitable dose of killed typhoid bacilli in rabbits causes, within twenty-four hours, a "refractory state" which enables them to withstand a dose of living typhoid that is fatal to a normal rabbit. The serums of these rabbits, however, show a distinct but not a marked bacteriolytic titer four and twenty-four hours, respectively, after such injections. They suggest that blood serum is more bactericidal than lymph, and that the vaccine injection causes a greater flow of bactericidal serum into the lymphoid organs and thus overcomes the local infection.

Culver² worked chiefly on gonococcal arthritic patients, ten of them received successive injections of proteose and six received killed gonococci. He was not able to find marked differences in results from these two groups of patients treated, nor did he find marked bactericidal

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1 Teaque, O., and McWilliams, H. I. The Bacteriolytic Power of Normal and Immune Rabbit Serum for Typhoid Bacilli and the Intravenous Injection of Vaccine upon the Same, *J. Immunol.* **2** 167, 185 (Feb.) 1917.

2 Culver, H. Antibodies in Gonococcal Arthritis, *J. Lab. & Clin. Med.* **3** 11 (Oct.) 1917.

titer changes in the serums of these patients within twenty-four hours after the administration of the proteins. He thinks that the antibody fluctuation caused by the intravenous injection, which produces a chill, might be explained by the motion of the affected part during the chill, and that it is not due directly to the foreign protein injection.

Bruck³ has suggested that the protein acts as a toxoid antigen which brings about the sensitization of cell receptors and the overproduction of similar sessile receptors, but which has lacked the necessary stimulus to cause the discharge of these receptors.

Recently, Herrmann,⁴ who has investigated this subject more fully, has shown that after the intravenous injection of ascitic fluid and human serum there is definite liberation of specific opsonin agglutinin in rabbits previously sensitized with streptococcus or meningococcus, and markedly so of lysin in those sensitized with sheep erythrocytes, while nonspecific protein has no effect on the rabbits previously sensitized with *Bacillus typhosus*. He concludes that the intravenous injection of foreign protein serves as a stimulus for the liberation of specific antibodies in animals in which the previously injected antigen is unable to cause such a liberation, the insufficiency may lie either in the antigen or in the rabbits.

Larson⁵ holds practically the same point of view as does Herrmann. He believes that many bacteria, such as pneumococcus and streptococcus, are imperfect antigens corresponding to the heated tetanus toxin, the toxoid. During the active processes of streptococcal or pneumococcal infection, these organisms act as stimuli to induce the cells to produce the specific antibodies against these specific organisms, but these imperfect antigens do not possess the second stimulus, the "exfoliative stimulus," the stimulus which causes the antibodies to be cast off from the cells into the blood circulation. This second stimulus, as Larson assumes, is supplied by the nonspecific agents, such as vaccines, foreign proteins and proteose. In other words, the antigen which stimulates the cells to produce antibodies is specific, while the agent which causes the cells to throw off the antibodies formed is not necessarily specific. From these premises, Larson draws his conclusion that the injection of foreign proteins enables the organism to throw off the so-called sessile antibodies and get them into the circulation.

³ Bruck, C. Experimentelle Beiträge zur Theorie der Immunität, Ztschr f Hyg u Infectskrankh **46** 48, 176, 1904.

⁴ Herrmann, S F. Liberation of Antibodies by Foreign Protein, J Infect Dis **23** 457 (Nov) 1918.

⁵ Larson, W P. Principles of Foreign Protein Therapy, Minnesota Med **2** 332 (Sept) 1919.

In spite of all these divergent observations and opinions, we may safely assume, in the way Petersen does,⁶ that

We may expect that if injections are made in patients who have been previously immunized that they will respond with an increase in the antibody titer of the serum, if they are injected during the course of the disease, antibodies which have been formed in the cells but not yet cast off may be "shed," as Larson has suggested, and we may then determine an increase in the serum. On the other hand, if they have been thrown into the circulation during the course of a disease as rapidly as formed, we cannot expect any increase in the titer. We may also assume that with the stimulation of the cellular activity ("plasma-activation") the cell will respond by producing an increased amount of antibodies if they still are capable of such response.

As antibodies, such as antitoxins, opsonins, agglutinins, bacteriolysins, hemolysins and other cytolysins are frequently found in the serums of normal persons and animals, we may be allowed to assume, too, that these antibodies, the "natural receptors," as they are present naturally in the organism, are capable of responding to the stimuli, and should suffer from the same fate, more or less, as those which are artificially produced, after an injection of a suitable dose of appropriate nonspecific protein agent. By using normal, instead of previously sensitized persons and animals as subjects for study, we may eliminate, to some extent, the possible influence which may rise from difference in degrees to which the persons or animals are sensitized. We thus are given a more adequate means to investigate the relative potency of various agents used in proteinotherapy and their selective, if any, influences on different antibodies.

PURPOSE OF INVESTIGATION

The study of the influence of various nonspecific agents on the thermoregulatory disturbances and the mobilization of leukocytes was given in a previous paper.⁷ The present interest has been devoted to a comparative study of the influence of various nonspecific agents on the mobilization of various native antibodies in the serums of normal persons and rabbits, using the same variety of agents as were used in the previous experiments.

PREPARATION OF AGENTS AND DOSAGE

Eight agents were used, and the size of the dosage depended on the weight of the patient or rabbit. They were as follows:

⁶ Petersen, W F Protein Therapy and Nonspecific Resistance, Ed 1, 1922, p 67

⁷ Ling, C Y Studies of the Mechanism of Reaction of Nonspecific Protein Agents in the Treatment of Disease I Influence of Various Agents on Temperature, Arch Int Med 35 598 (May 15) 1925

1 Sterile distilled water 0.1 cc per kilogram of weight for human being, 1 cc per kilogram of weight for rabbit, given intravenously

2 Autoserum 0.5 cc per kilogram of weight for human being and rabbit, intravenously

3 Sterile horse serum 0.2 cc per kilogram of weight for human being and rabbit, given intravenously

4 Certified milk with a bacterial count of from 7,000 to 10,000, boiled for ten minutes 0.2 cc per kilogram of weight for human being and rabbit, given intramuscularly

5 Market milk, with bacterial count of from 300,000 to 400,000, boiled for ten minutes 0.2 cc per kilogram of weight for human being and rabbit, given intramuscularly

6 Crotalins: $\frac{1}{15,000}$ grain per kilogram of weight for human being and $\frac{1}{3,000}$ grain per kilogram of weight for rabbit, dissolved in saline solution and given hypodermically. The material was kindly supplied by Dr. Spangler of Philadelphia.

7 Peptone, a 1 per cent solution in physiologic sodium chloride solution, autoclaved for twenty minutes 0.02 cc per kilogram of weight for human being and rabbit, given intravenously

8 Typhoid vaccine, consisting of 100,000,000 heat killed organisms suspended in saline solution 0.2 cc per kilogram of weight for human being and rabbit, given intravenously

ANTIBODIES STUDIED

Three specimens of blood were obtained from each patient or rabbit before and four and twenty-four hours, respectively, after the administration of the agent. The serums obtained were subjected to the following studies:

1 Serum titer of the bactericidal activity against *Bacillus typhosus*

2 Serum titer of the bactericidal activity against *Staphylococcus aureus*

3 Bacteriolytic value of the serum in phagocytic activity for *Staphylococcus aureus*

4 Serum titer of natural hemolysin in hemolytic activity against sheep erythrocytes

5 Serum titer of complement in hemolytic activity against sheep erythrocytes

BACTERIOLOGIC TECHNIC

Bacteriolytic Titration—The method devised by Lacy and Heist,⁸ for determining the bactericidal power of the coagulable blood against pneumococcus was principally used in bacteriolytic titration for *B. typhosus*.

⁸ Heist, G. D., Solis-Cohen, S., and Solis-Cohen, M. Bactericidal Action of Whole Blood, *J. Immunol.* **3**, 261 (July) 1918.

and *Staphylococcus aureus*. Typhoid suspension was a culture (Rawling's) grown for twenty-four hours in nutrient bouillon at 37.5°C.

In applying the Lacy-Heist method to this laboratory culture, it was found that the coagulable blood of normal persons or rabbits would, in most instances, entirely prohibit the growth of this organism, even when the latter was used in undiluted form. Furthermore, it also was found that the bactericidal titer varies considerably in the serum of each individual subject studied.

For these reasons, the approximate value of the serum of each individual subject was preliminarily estimated by setting up varying dilutions of serum with the standard typhoid suspension (10,000,000,000 per cubic centimeter), using Wright's many stemmed pipet method. After twenty-four hours' incubation, the lowest serum which showed no inhibition of bacterial growth was taken as the fiducial serum dilution, like which, for the regular comparative tests, all those specimens taken from one particular individual subject were prepared.

Each of these three serum dilutions was then set up with the five varying strengths of the standard typhoid suspension (10,000,000,000 per cubic centimeter), viz., undiluted, 1/5, 1/25, 1/125 and 1/625, following closely the technic as described by Lacy-Heist for pneumococcus.

The bactericidal activity of the serum was measured by the strength of the bacterial suspension in which the growth was prohibited, and the comparative value of the bactericidal serum was expressed in terms of times of the weakest bacterial suspension used (1/625), which is designated as 1. Thus, if 1/125 is the lowest dilution in which the growth is found inhibited, the bactericidal value will be 1/125 divided by 1/625, which equals 5.

For *Staphylococcus aureus*, a suspension of 500,000,000 per cubic centimeter was used as standard from which undiluted, 1/5, 1/25, 1/125 and 1/625 dilutions were prepared. Coagulable blood was used, employing the Lacy-Heist method without modification. The bactericidal value was recorded as for typhoid bacillus.

Bacteriotoxic Titration.—The method described by Evans,⁹ as used in the Hygienic Laboratory for standardizing the antimeningococcus serum, was employed in these tests for estimating the bacteriotoxic value of the serum in phagocytic activity of leukocytes for *Staphylococcus aureus*. Bacteriotoxic serum was prepared in undiluted, 1/5, 1/10 and 1/20 dilutions. Staphylococci, which had been grown for twenty-four hours, were washed off from the agar slants and suspended in Locke's solution (10,000,000,000 per cubic centi-

⁹ Evans, A. C. The Tropin Reactions of Antimeningococcus Serum, Bull. Hyg. Lab., U. S. P. H. S., No. 124, p. 43, (Nov.) 1920.

meter) Living leukocytes were secured intrapleurally from a rabbit which had been previously injected with aleuronat emulsion (starch, 3 gm, aleuronat, 5 gm, and ordinary broth, 100 c.c.) After being thoroughly washed with warm citrate solution and Locke's solution, the leukocytes were suspended in Locke's solution also Serum dilutions, bacterial suspensions and leukocytic suspensions were all used in 0.2 c.c. amounts each

Bacterial suspension and serum dilution were first mixed and incubated in a water bath (37.5°C.) for forty-five minutes The leukocytic suspension was then added, and it was reincubated for another forty-five minutes The smears were then quickly made from each tube and stained A leukocyte control which carried in it leukocytic suspension and bacterial suspension and saline solution also was included

The highest serum dilution with which more than 32 per cent of the leukocytes showed active phagocytosis was read as titer for the serum The latter was recorded in terms of its titer dilution only when the number of phagocytic leukocytes counted exceeded at least twice those observed from the leukocyte control tube due to spontaneous phagocytosis

Titration of Antisheep Cell Serum Hemolysin—The hemolytic system consisted of 1 c.c. of 1:20 guinea-pig complement, 1 c.c. of 2 per cent sheep cell suspension and a dose of inactivated serum varying from 0.2 c.c., 0.4 c.c., to 1.2 c.c. The one-hour incubation method in a water bath was employed The smallest amount of serum dilution which brought about complete hemolysis was taken as the hemolytic unit of the serum, and the relative value was recorded in terms of number of units per cubic centimeter of serum tested

Titration of Antisheep Cell Serum Complement—For these tests, a permanent standard solution of antisheep hemolysin, with its unit previously determined by titrating it against 1 c.c. of 2 per cent sheep cell suspension and 1 c.c. of 1:20 guinea-pig complement, was used throughout

Natural antisheep hemolysin, which might be present in the serums tested, was first absorbed and removed by mixing 2 parts of the unheated serum with 8 parts of 2.5 per cent sheep cell suspension at 0°C. for fifteen minutes, and the supernatant serum dilution, which was then 1:5, secured by centrifugation

The hemolytic system for complement titration consisted then of 2 units of standard hemolysin, 1 c.c. of 2 per cent sheep cell suspension and a dose of antisheep cell hemolysin-free serum dilution (1:5), varying from 0.2 c.c., 0.4 c.c., to 1.6 c.c.

The smallest amount of serum dilution which causes complete hemolysis after one hour's incubation is designated as the complement unit of the serum, and the relative value is recorded in terms of the number of units per cubic centimeter of serum.

TABLE 1.—*Influence of Various Agents on Bactericidal Activity of Serums of Normal Human Being and Rabbit*

Agents	Times Examinations Were Made	Results Obtained with <i>B Typhosus</i>				Results Obtained with <i>Staphylococcus Aureus</i>				Mean Average*
		Rabbit	Human Being	Average	Mean Average*	Rabbit	Human Being	Average	Mean Average*	
Distilled water	Before injection	15.0	5.0	10.0	50.0	0.5	5.0	2.8	50.0	
	4 hours after injection	2.5	0.5	1.5	44.5	0.5	5.0	2.8	50.0	
	24 hours after injection	75.0	5.0	40.0	80.0	13.0	1.0	7.0	54.2	
Autoserum	Before injection	2.5	5.0	3.7	50.0	25.0	1.0	13.0	50.0	
	4 hours after injection	25.0	1.0	13.0	59.3	3.0	1.0	2.0	39.0	
	24 hours after injection	30.0	25.0	27.5	73.3	25.0	25.0	25.0	62.0	
Horse serum	Before injection	40.0	25.0	32.5	50.0	5.0	5.0	5.0	50.0	
	4 hours after injection	45.0	5.0	25.0	42.5	2.5	1.0	1.8	46.8	
	24 hours after injection	40.0	25.0	32.5	50.0	43.0	25.0	34.0	79.0	
Certified milk	Before injection	10.0	5.0	7.5	50.0	1.0	5.0	3.0	50.0	
	4 hours after injection	50.0	1.0	25.5	68.0	5.0	1.0	3.0	50.0	
	24 hours after injection	10.0	25.0	17.5	60.0	1.0	25.0	13.0	60.0	
Market milk	Before injection	5.0	5.0	5.0	50.0	1.0	1.0	1.0	50.0	
	4 hours after injection	8.0	25.0	16.5	61.5	13.0	18.3	15.7	64.7	
	24 hours after injection	58.0	25.0	83.0	128.0	5.0	5.0	5.0	54.0	
Crotaln	Before injection	63.0	5.0	74.0	50.0	78.0	5.0	41.5	50.0	
	4 hours after injection	13.0	25.0	19.0	35.0	75.0	5.0	40.0	48.5	
	24 hours after injection	125.0	25.0	75.0	91.0	80.0	15.0	47.5	56.0	
Peptone	Before injection	2.5	5.0	3.8	50.0	63.0	5.0	34.0	50.0	
	4 hours after injection	0.5	1.0	0.8	47.0	13.0	5.0	9.0	25.0	
	24 hours after injection	3.0	5.0	4.0	50.2	75.0	25.0	50.0	66.0	
Typhoid vaccine	Before injection	12.0	5.0	8.5	50.0	1.0	1.0	1.0	50.0	
	4 hours after injection	15.0	5.0	10.0	51.5	1.0	25.0	13.0	62.0	
	24 hours after injection	125.0	25.0	75.0	116.5	15.0	25.0	20.0	69.0	
Control	First examination	3.0	5.0	4.0	50.0	3.0	1.0	2.0	50.0	
	Second examination	3.0	5.0	4.0	50.0	3.0	1.0	2.0	50.0	
	Third examination	25.0	5.0	15.0	61.0	12.5	5.0	9.0	57.0	

* The value of bactericidal serums taken before administration is arbitrarily set at 50, the increase or decrease in value of those taken four hours and twenty-four hours after is thus added or subtracted therefrom.

RESULTS

The results of these experiments and the composite results obtained from both human subjects and rabbits are given in Tables 1, 2 and 3. Their relative values are expressed in Charts 1, 2, 3 and 4. The study may be summarized as follows:

*Influence on Bactericidal Power of Serum for *Bacillus Typhosus*.*—Apparently all the agents used influence, to some extent, the bactericidal titer within twenty-four hours after the administration. It depends, in the first place, on the nature of the protein agent used. The steady increase of serum titer, after the injections of typhoid vaccine and market milk that is rich in bacterial content, seems to indicate the great potency of some proteins of bacterial origin in producing the nonspecific resistance against typhoid infection. Secondly, the bactericidal serum titer is also undoubtedly influenced by the mere drawing of blood from the animal.

and the trauma resulting therefrom, which acts in the same way as a mild form of nonspecific protein agent, as evidenced by the results obtained from human and rabbit controls. Lastly, no two animals react alike, allowances have to be given, of course, to individual differences (Table 1, Chart 1).

*Influences on Bactericidal Power of Serum for *Staphylococcus Aureus*.*—The same results as those with *B. typhosus* are observed so far as the greater potency of bacterial proteins and the phenomena of venesection reactions are concerned. The individual variations are

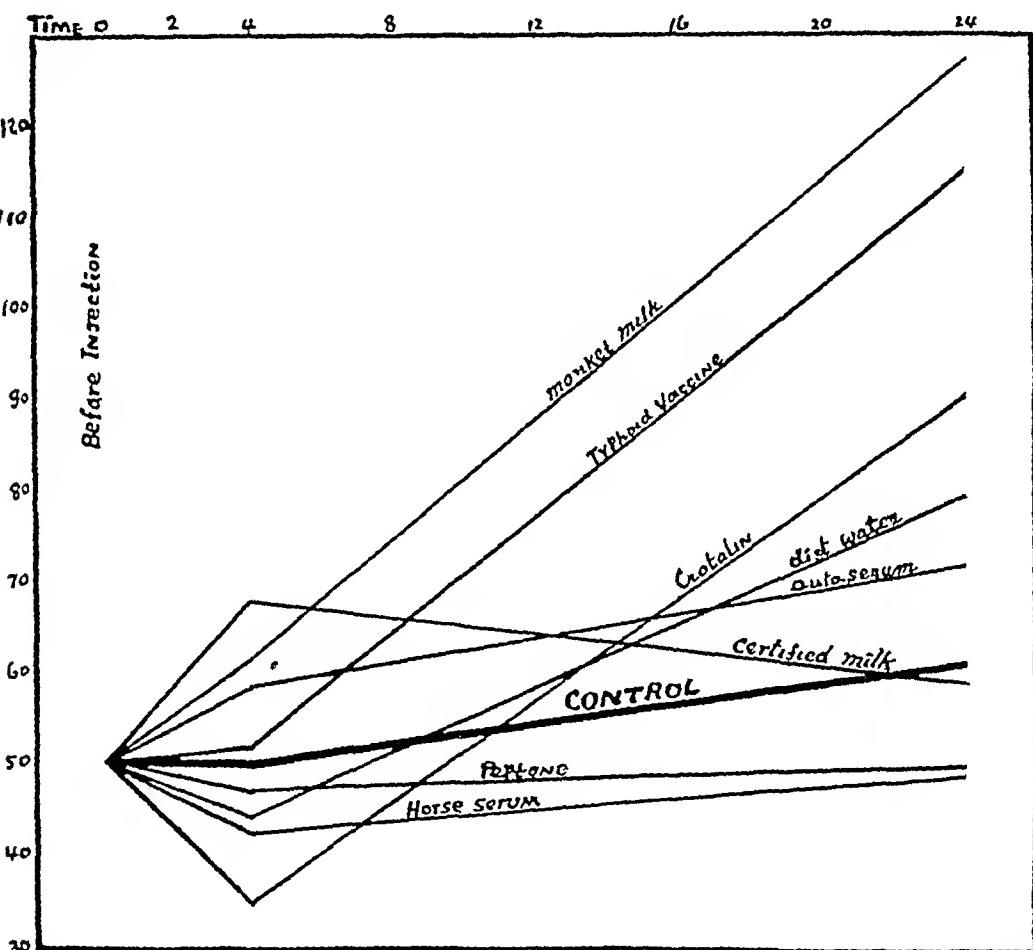


Chart 1.—Composite results of influence of various agents on bactericidal activity of serums of human being and rabbit for *Bacillus typhosus*

probably the explanation for the results observed in those treated with horse serum and peptone (Table 1, Chart 2).

*Influence on the Bacteriotropic Content of Serum in Phagocytic Activity for *Staphylococcus Aureus*.*—The opsonin titer which shows decided increase, as observed four hours after injection, in those treated with peptone, market milk and typhoid vaccine, has the tendency to resume its usual, or normal, opsonin level in about twenty-four hours after administration, while, on the contrary, decided drops of

titer, persisting for more than twenty-four hours, are seen in those treated with autoserum, crotalim and certified milk. Apparently, there is a decided increase of opsonin content in the serum sometimes within the period of four hours after the administration of any of the agents studied. After the maximum of this transient rise of opsonin titer has been reached, it quickly comes down to normal or even to subnormal, in about twenty-four hours after the treatment (Table 2, Chart 3)

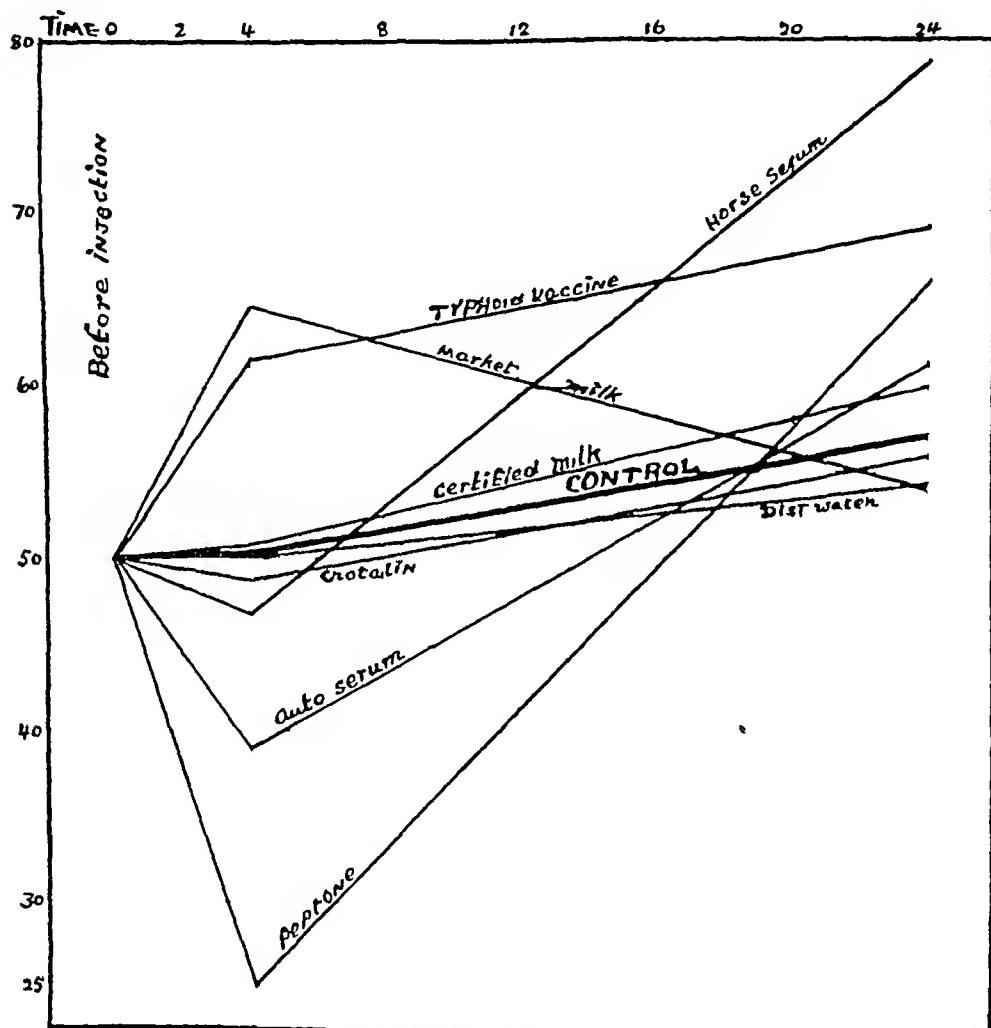


Chart 2—Composite results of influence of various agents on bactericidal activity of serums of human being and rabbit for *Staphylococcus aureus*

Influence on Antisheep Hemolysin and Antisheep Hemolytic Complement—The effect of protein treatment on the antisheep hemolysin content of serum is very slight, if any, as shown in these experiments. Not infrequently, the normal serums, either human or rabbit, were found to be practically free from the natural antisheep hemolysin, by the method employed. The fluctuation of complement content, however, is decidedly noticeable and after a fairly constant manner. Apparently, the introduction of one dose of foreign protein has called for the

TABLE 2—*Influence of Various Agents on the Serum Bacteriolytic Activity for Staphylococcus Aureus*

Agents	Times Examinations Were Made	Rabbit	Human Being	Average	Mean Average*
					*
Distilled water	Before injection	15.0	10.0	12.5	10.0
	4 hours after injection	3.0	20.0	11.5	9.0
	24 hours after injection	10.0	20.0	15.0	12.5
Autoserum	Before injection	7.5	20.0	13.8	10.0
	4 hours after injection	3.0	20.0	11.5	7.7
	24 hours after injection	2.5	14.0	8.0	4.2
Horse serum	Before injection	1.0	20.0	10.5	10.0
	4 hours after injection	7.5	10.0	9.0	8.5
	24 hours after injection	3.0	20.0	11.5	11.0
Certified milk	Before injection	1.0	10.0	5.5	10.0
	4 hours after injection	7.5	10.0	9.0	13.5
	24 hours after injection	5.0	20.0	12.5	7.0
Market milk	Before injection	3.0	10.0	6.5	10.0
	4 hours after injection	7.0	20.0	13.5	17.0
	24 hours after injection	10.0	10.0	10.0	13.5
Crotalins	Before injection	12.0	10.0	11.0	10.0
	4 hours after injection	17.0	5.0	11.0	10.0
	24 hours after injection	6.0	5.0	5.5	4.5
Peptone	Before injection	3.0	5.0	4.0	10.0
	4 hours after injection	12.5	10.0	11.5	17.5
	24 hours after injection	5.5	10.0	8.0	14.0
Typhoid vaccine	Before injection	5.0	5.0	5.0	10.0
	4 hours after injection	4.0	10.0	7.0	12.5
	24 hours after injection	5.0	10.0	7.5	12.5
Control	First examination	12.5	7.5	10.0	10.0
	Second examination	12.0	15.0	13.5	13.5
	Third examination	13.2	10.0	11.6	11.6

* The bacteriolytic value of the serums taken before administration is arbitrarily set at 10, the increase or decrease in value of those examined four hours and twenty-four hours after is thus added or subtracted therefrom.

TABLE 3—*Influence of Various Agents on Serum Hemolysis Content and Serum Complement Content in Hemolytic Activity for Sheep Erythrocytes*

Agents	Times Examinations Were Made	Serum Hemolysin				Serum Complement				Mean
		Rabbit	Human Being	Average	Mean Average*	Rabbit	Human Being	Average	Mean Average*	
Distilled water	Before injection	5.0	2.5	3.8	5.0	2.0	1.4	1.7	5.0	
	4 hours after injection	5.0	2.5	3.8	5.0	1.7	1.1	1.4	4.7	
	24 hours after injection	5.0	2.5	3.8	5.0	2.0	1.3	1.65	4.95	
Autoserum	Before injection	5.0		2.5	5.0	1.0	1.3	1.15	5.0	
	4 hours after injection	5.0		2.5	5.0	1.0	1.3	1.15	5.0	
	24 hours after injection	3.5		1.8	4.3	1.1	1.7	1.4	5.25	
Horse serum	Before injection	1.0		0.5	5.0	1.1	1.3	1.2	5.0	
	4 hours after injection	1.0		0.5	5.0	1.1	1.3	1.2	5.0	
	24 hours after injection	1.0		0.5	5.0	1.3	1.7	1.5	5.3	
Certified milk	Before injection	2.5	2.5	2.5	5.0	1.3	1.3	1.3	5.0	
	4 hours after injection	2.2	2.5	2.4	4.9	1.3	1.3	1.3	5.0	
	24 hours after injection	2.5	2.5	2.5	5.0	1.4	1.4	1.4	5.1	
Market milk	Before injection	3.3	2.5	2.9	5.0	1.0	1.4	1.2	5.0	
	4 hours after injection	3.0	2.5	2.8	4.9	0.8	1.3	1.05	4.9	
	24 hours after injection	3.3	2.5	2.9	5.0	1.0	1.4	1.2	5.0	
Crotalins	Before injection	2.0		1.0	5.0	2.0	1.0	1.5	5.0	
	4 hours after injection	2.0		1.0	5.0	1.7	0.8	1.25	4.75	
	24 hours after injection	2.0		1.0	5.0	2.0	1.0	1.5	5.0	
Peptone	Before injection	1.0	1.0	1.0	5.0	1.1	1.1	1.1	5.0	
	4 hours after injection	1.0	1.0	1.0	5.0	1.0	0.8	0.9	4.8	
	24 hours after injection	1.0	1.0	1.0	5.0	1.1	1.0	1.05	4.95	
Typhoid vaccine	Before injection	0.5	2.0	1.3	5.0	1.3	1.1	1.2	5.0	
	4 hours after injection	0.5	2.0	1.3	5.0	1.1	1.1	1.1	4.9	
	24 hours after injection	0.5	2.0	1.3	5.0	1.3	1.3	1.3	5.1	
Control	First examination	2.0	0.5	1.3	5.0	1.3	0.8	1.05	5.0	
	Second examination	2.0	0.5	1.3	5.0	1.3	0.8	1.05	5.0	
	Third examination	2.0	0.5	1.3	5.0	1.6	0.8	1.2	5.15	

* The serum titer of the serums examined before administration is arbitrarily set at 5 units per cubic centimeter, the increase or decrease at two subsequent examinations is thus added or subtracted therefrom.

sacrifice of the nonspecific serum complement during a period of about four hours directly after the administration, as evidenced by the decided drop of antisheep hemolytic content of serum, shown in these experiments. The complement titer is thence gradually recovered to its original amount, or slightly in excess, in about twenty-four hours.

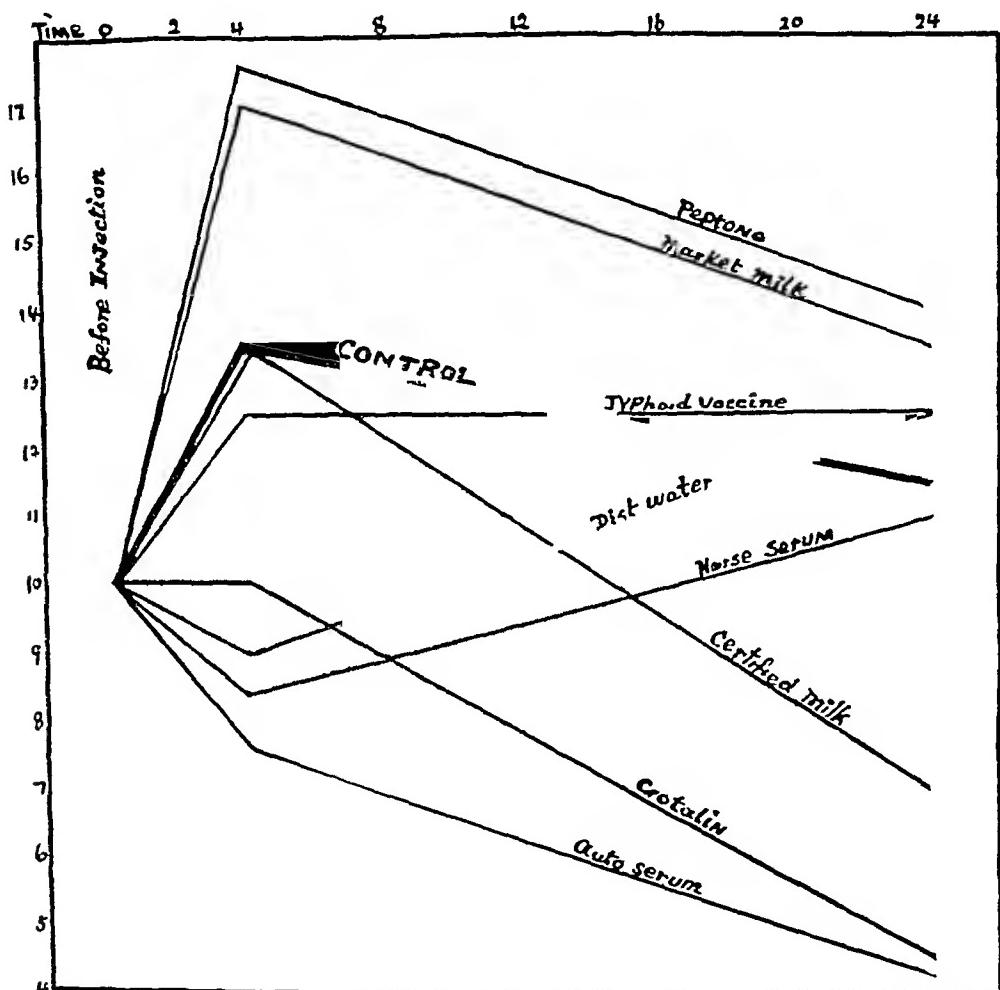


Chart 3—Composite results of influence of various agents on serum bacteriotropin in phagocytic activity for *Staphylococcus aureus*.

CONCLUSIONS

1 Natural serum antibodies, including bacteriolysin for *B. typhosus* and *Staphylococcus aureus*, bacteriotropin for *Staphylococcus aureus* in phagocytic activity, and antisheep hemolytic complement, but not antisheep hemolysin, are either mobilized or caused to be "shed" from the organism to some extent, within twenty-four hours, by an injection of any of the following agents distilled water, autoserum, horse serum, certified milk, market milk, crotalins, peptone and typhoid vaccine.

2 Bacterial proteins as represented by typhoid vaccine and market milk that is rich in bacteria, are found to be the most efficient agents for

producing a more decided and persistent increase of bacteriolysin against *B. typhosus* and *Staphylococcus aureus*

3. Peptone and high bacterial count market milk cause an increase of opsonic index in phagocytic activity against *Staphylococcus aureus* to the highest degree

4 Various agents have no effect on the serum content of natural antisheep hemolysin

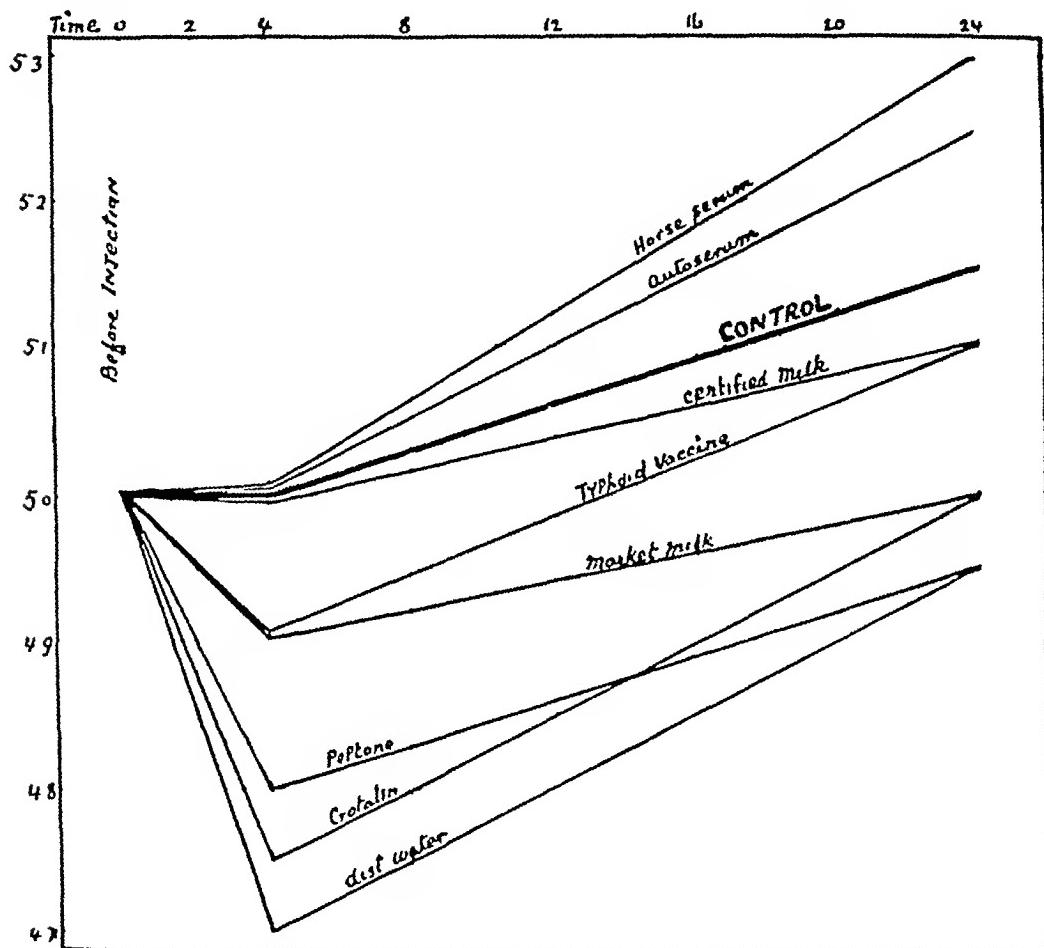


Chart 4—Composite results of influence of various nonspecific protein agents on serum complement in antisheep erythrocyte hemolytic activity

5 In general, antisheep hemolytic complement content of serum is reduced after protein treatment, and the reduction persists for more than twenty-four hours, its greatest decrease being sometime between injection and about four hours after, while its recovery to normal or even to slightly above normal level, as is found, in this case, in the serum under the influence of horse serum and autoserum, is about twenty-four hours after the administration

6 Bleeding the animal and the slight trauma resulting therefrom also will act as a mild form of nonspecific protein agent, which will likewise cause the nonspecific response

THE MECHANISM OF REACTION OF NONSPECIFIC PROTEIN AGENTS IN THE TREATMENT OF DISEASE

III THE INFLUENCE OF VARIOUS AGENTS ON THE MOBILIZATION OF BLOOD ENZYMES IN NORMAL PERSONS AND IN RABBITS¹

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In the blood stream, several proteolytic enzymes are known to occur. These include at least two leukoproteases which are capable of splitting native proteins largely to the proteose stage, and an erepsin-like enzyme freely hydrolyzing proteins from the intermediate stages (albumose and peptone) to the amino-acid forms. These enzymes seem to be derived from the disintegrating but not from living polymorphonuclear leukocytes, and fluctuations in the peripheral leukocyte count are not indicative of the relative titer of the enzyme concentration.¹

Apart from leukocytes as the chief sources of proteolytic enzymes present in normal blood, small amounts of various digestive enzymes may be derived from gastro-intestinal tracts, the large abdominal organs and from areas altered pathologically if at all. They enter the blood stream possibly by way of the lymph current. These include a tryptase or protease, a polyvalent trypsin-like ferment capable of splitting native proteins all the way down to their lowest split products, if the anti-ferments are removed, a serum ereptase or peptidase hydrolyzing partly digested proteins to amino-acids and a lipase that splits the fats. That serum contents of these enzymes are readily influenced by diet has been shown by Jobling, Petersen and Eggstein.²

In normal blood, these enzymes are present in small amounts, but when foreign proteins are introduced into the system, enzyme activities are found to be excessively increased. Foreign protein may be in the form of living bacteria, as in the case of infection, invading, as they do, the system. It may be in the form of vaccines, toxins or serums, as those are used in immunologic inoculations and in protein therapy. These excessive enzymes are either elaborated by body cells as a defensive response to the protein stimuli or derived from gastro-intestinal tracts,

¹ From the Department of Bacteriology and Immunology, Graduate School of Medicine of the University of Pennsylvania

1 Petersen, W F. The Ferment-Antifерment Balance and Its Relation to Therapeusis, Arch Int Med **20** 515 (Oct) 1917 Hedm, S G Ueber proteolytische Enzyme im Harn, Ztschr f physiol Chem **112** 252, 1921

2 Jobling, J W, Petersen, W F, and Eggstein, A A Serum Ferment and Antifерment After Feeding, J Exper Med **22** 129, 1915

owing to accelerated lymph flow accompanying the protein shock, or they may be derived from both³ The fact cannot be entirely established at present

These blood ferments, from whatever sources they may be, must have played an important rôle in aiding to digest, destroy and finally to eliminate entirely from the system the noxious materials

Proteins are known to be more or less toxic only when they are belonging to or have been hydrolyzed to a certain split stage. Various peptones are supposed to be most toxic to the system. Vaughan's belief that bacterial intoxication was due to enzyme digestion of infective materials was based on this. On the other hand, if the enzymes, with which we are richly supplied, are capable of splitting toxic materials further on to nontoxic stages, toxins liberated would thus be detoxicated as fast as they are formed. The disease foci are thus gradually and favorably influenced in this way, and without leading the patient to a state of undesired intoxication. In connection with this, Petersen and Short, in studying pneumonia that terminates by crisis or by lysis, were able to observe invariably an increase of ereptase titer in the blood, either preceding or accompanying the clinical changes.⁴

Had these facts been established, our success in using nonspecific proteins in the treatment of infectious diseases would depend on the right kind of agents, which would bring about an increase of various blood enzymes and in their desired proportions.

By using normal persons and normal rabbits, free from any detectable disease foci, by taking precautions to avoid the possible effect of diet, and by employing the commonly recognized dosage, a favorable approach is offered to the study of the potencies of various protein agents used to produce an increase in blood enzyme activities.

PURPOSE OF INVESTIGATION

Comparative studies of the influence of various nonspecific protein agents (given below) on the thermoregulatory center and the mobilization of blood leukocytes and antibodies in normal persons and rabbits were given in two previous papers.⁵ The influence of the same agents on the enzyme activities of blood in normal persons and rabbits is to be summarized in this paper.

³ Jobling, J. W., Petersen, W. F., and Eggstein, A. A. The Mechanism of Anaphylactic Shock, Studies on Ferment Action, *J. Exper. Med.* **22** 401, 1915

⁴ Petersen, W. F., and Short, C. A. On the Relation of the Serum Erep-tase (Peptidase) Titer to the Clinical Course in Pneumonia, *J. Infect. Dis.* **22** 142 (Feb.) 1918

⁵ Ling, C. Y. The Mechanism of Reaction of Nonspecific Protein Agents in the Treatment of Disease I. Influence of Various Agents on Temperature, *Arch. Int. Med.* **35** 598 (May 15) 1925 II. Influence of Various Agents on Mobilization of Blood Antibodies, *ibid.*, this issue

NONSPECIFIC AGENTS AND DOSAGE

Eight agents and the doses used were the same as used in the previous experiments. They may be recapitulated as follows:

1 Sterile distilled water 0.1 cc per kilogram of weight for human being, 1 cc per kilogram of weight for rabbit, given intravenously.

2 Autoserum 0.5 cc per kilogram of weight for human being and rabbit, given intravenously.

3 Sterile horse serum 0.2 cc per kilogram of weight for human being and rabbit, given intravenously.

4 Certified milk with a bacterial count of from 7,000 to 10,000, boiled for ten minutes 0.2 cc per kilogram of weight for human being and rabbit, given intramuscularly.

5 Market milk, with a bacterial count of from 300,000 to 400,000, boiled for ten minutes 0.2 cc per kilogram of weight for human being and rabbit, given intramuscularly.

6 Crotalim $\frac{1}{15}$ 000 grain per kilogram of weight for human being and $\frac{1}{3}$ 000 grain per kilogram of weight for rabbit, dissolved in saline solution and given hypodermically. The material was supplied by Dr Spangler of Philadelphia.

7 Peptone, a 1 per cent solution in physiologic sodium chloride solution, autoclaved for twenty minutes 0.02 cc per kilogram of weight for human being and rabbit, given intravenously.

8 Typhoid vaccine, consisting of 100,000,000 heat killed organisms suspended in saline solution 0.2 cc per kilogram of weight for human being and rabbit, given intravenously.

ENZYMES STUDIED

To avoid the possible effect of diet on the fluctuation of blood enzymes, all examinations were made in the morning before food was given. Untreated individuals used for controls were examined in the same way. Three blood specimens were taken, before, four hours after, and twenty-four hours after treatment. Each serum obtained was subjected to the following enzyme determinations:

1 Degree of the proteolytic activity of serum, in digesting its own native proteins present in the serum.

2 Degree of the peptolytic activity of serum in digesting a given amount of peptone solution.

3 Degree of lipolytic activity of serum in digesting a given amount of ethyl butyrate.

TECHNIC

Proteolytic Technic—The technic employed in these enzyme tests was principally that described by Petersen. The method employed for studying the proteolytic activity is briefly as follows: 15 cc of hemoglobin free serum and 3 cc of chloroform were thoroughly mixed in a graduated test tube (3 cm in diameter). Chloroform was added here to hold in check the serum anti-enzyme action. A control tube that carried in it 15 cc of serum, with 2 drops of toluene added as preservative, was inactivated at 60°C for thirty minutes. This control tube and the sample tube were incubated at 37.5°C for forty-eight hours, tubes being shaken at regular intervals. One cubic centimeter of a mixture of 10 per cent acetic acid plus 20 per cent sodium chloride solution was then added to each tube. To remove the chloroform, the tube was gently heated in a water bath. When the chloroform was entirely evaporated from the sample tube, 4 cc of water was added to each tube, and the temperature was raised to the boiling point, and kept at such for ten minutes. When cooled, sufficient water was added to make up a total volume of 15 cc. Coagulable proteins were filtered off. Ten cubic centimeters of filtrate, equivalent to 1 cc of serum, was then secured. The total nitrogen content was determined according to Kjeldahl's method. The difference in milligrams of uncoagulable nitrogen between 100 cc of sample serum and 100 cc of control serum expresses the proteolytic enzyme units.

Peptolytic Technic—In five test tubes, 1 cc of the following serum dilutions were prepared: Undiluted, 1/2, 1/4, 1/8 and 1/16. To each tube, 1 cc of 4 per cent peptone solution and 1 cc of toluene were added. They were then incubated at 37.5°C for eighteen hours. Bromin water was then introduced into each tube, drop by drop, until the pink color appeared. The reciprocal of the highest serum dilution that shows the pink color expresses the peptolytic enzyme units.

Lipolytic Technic—One cubic centimeter of serum, 1 cc of ethyl butyrate, 0.5 cc of toluene, and a sufficient amount of physiologic sodium chloride solution to bring the total volume up to 10 cc were mixed thoroughly in a flask. A serum control and a peptone control were also included. The tubes were incubated at 37°C for four hours. Twenty-five cubic centimeters of neutral alcohol was then added to each flask. The acidity developed was titrated to faint pink with hundredth normal sodium hydroxid, using phenolsulphonephthalein solution as indicator. After the result obtained is deducted from the control, the number in cubic centimeters of hundredth normal sodium hydroxid, used to neutralize the acidity developed by 1 cc of serum from 1 cc of ethyl butyrate, expresses the lipolytic units.

TABLE 1.—Influence of Various Agents on Serum Proteolytic Enzymes

Agents	Times Examinations Were Made	Rabbit	Human Being	Average	Mean Average*
Distilled water	Before injection	35	21	28	40
	4 hours after injection	21	07	14	26
	24 hours after injection	63	14	39	51
Autoserum	Before injection	45	35	40	40
	4 hours after injection	14	27	21	21
	24 hours after injection	35	24	30	30
Horse serum	Before injection	14	21	18	40
	4 hours after injection	14	35	25	47
	24 hours after injection	11	14	13	35
Certified milk	Before injection	14	14	14	40
	4 hours after injection	14	07	11	37
	24 hours after injection	07	28	18	44
Market milk	Before injection	23	28	26	40
	4 hours after injection	37	14	26	40
	24 hours after injection	42	28	35	49
Crotalins	Before injection	140	07	74	40
	4 hours after injection	124	08	66	32
	24 hours after injection	141	14	78	44
Peptone	Before injection	34	28	31	40
	4 hours after injection	50	56	53	62
	24 hours after injection	28	28	28	37
Typhoid vaccine	Before injection	70	14	42	40
	4 hours after injection	56	35	46	44
	24 hours after injection	28	07	18	16
Control	First examination	28	34	31	40
	Second examination	20	18	19	28
	Third examination	30	40	35	44

* The proteolytic activity expressed in terms of units, obtained from the specimen taken before injection, is arbitrarily set at 4, the increase or decrease at two subsequent examinations is added to or subtracted from it.

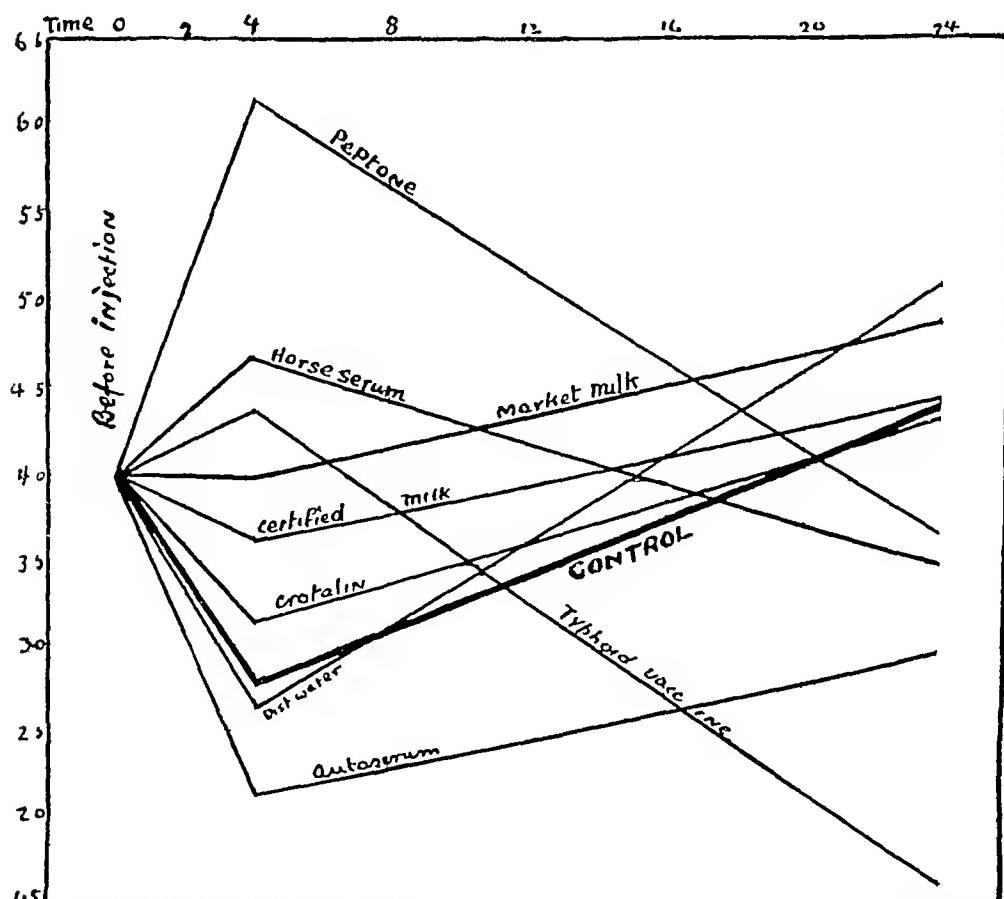


Chart 1—Composite results of influence of various agents on proteolytic enzymes in blood of human being and rabbit

RESULTS

The composite results of these experiments are given in Tables 1 and 2 and in Charts 1, 2 and 3. A brief survey of this study may be summarized as follows:

Influence on Proteolytic Activities—The proteolytic enzymes acted well but slowly at 37.5°C., incubation for not less than forty-eight hours will insure better results. Practically all the agents used influenced fluctuation of protease content of blood some time between four and twenty-four hours after the injection. Peptone induced a marked and an early response, while market milk and distilled water produced a slower but more persistent increase (Table 1 and Chart 1).

Influence on Peptolytic Activities—The relative values of peptolytic activities obtained by the method employed were only approximately but not absolutely accurate, as inconsistent readings were not infrequently found to occur. As a whole, however, they did definitely indicate a steady increase of peptidase titer in about, or more than, twenty-four hours after injection, while the initial depression was prolonged to about four hours after injection (Table 2 and Chart 2).

TABLE 2.—*Influence of Various Agents Mobilization of Peptolytic and Lipolytic Enzymes (Human)*

Agents	Times Examinations Were Made	Peptolytic Activity		Lipolytic Activity	
		Units	Mean Average*	Units	Mean Average*
Distilled water	Before injection	8.0	10.0	11.0	10.0
	4 hours after injection	8.0	10.0	9.0	8.0
	24 hours after injection	12.0	14.0	10.0	9.0
Autoserum	Before injection	8.0	10.0	11.0	10.0
	4 hours after injection	4.0	6.0	8.0	7.0
	24 hours after injection	12.0	14.0	10.5	9.5
Horse serum	Before injection	8.0	10.0	7.0	10.0
	4 hours after injection	10.0	12.0	9.0	12.0
	24 hours after injection	14.0	16.0	6.0	9.0
Certified milk	Before injection	14.0	10.0	5.6	10.0
	4 hours after injection	14.0	10.0	6.0	10.4
	24 hours after injection	20.0	16.0	6.5	10.9
Market milk	Before injection	14.0	10.0	6.0	10.0
	4 hours after injection	16.0	12.0	6.0	10.0
	24 hours after injection	20.0	16.0	7.0	11.0
Crotalins	Before injection	14.0	10.0	8.0	10.0
	4 hours after injection	12.0	8.0	7.0	9.0
	24 hours after injection	20.0	16.0	7.0	9.0
Peptone	Before injection	18.0	10.0	6.0	10.0
	4 hours after injection	14.0	6.0	5.0	9.0
	24 hours after injection	24.0	16.0	7.0	11.0
Typhoid vaccine	Before injection	8.0	10.0	6.0	10.0
	4 hours after injection	2.0	4.0	7.0	11.0
	24 hours after injection	14.0	16.0	5.0	9.0
Control	First examination	8.0	10.0	8.0	10.0
	Second examination	6.0	8.0	7.2	9.2
	Third examination	10.0	12.0	8.2	10.2

* The peptolytic or lipolytic units obtained from specimens obtained before injection are arbitrarily set at 10, the increase or decrease at two subsequent examinations is added to or subtracted from it.

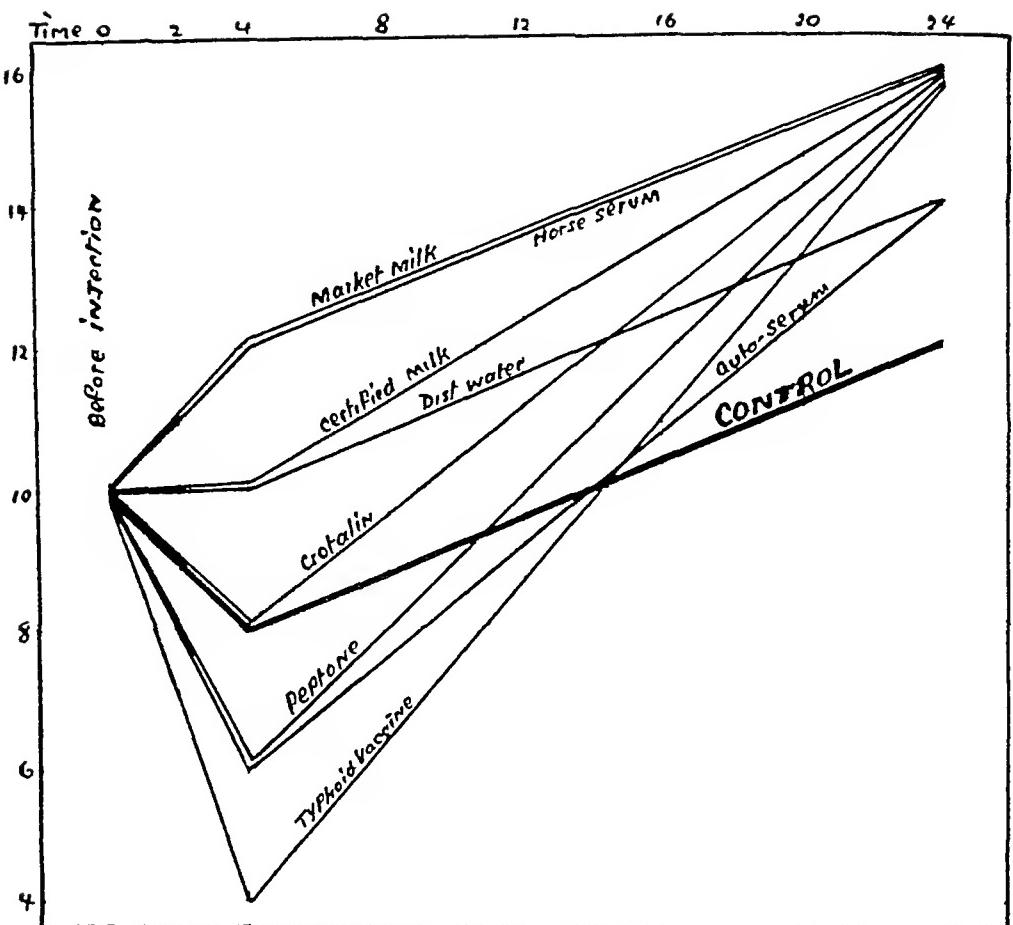


Chart 2—Composite results of influence of various agents on peptolytic enzymes in blood of human being and rabbit

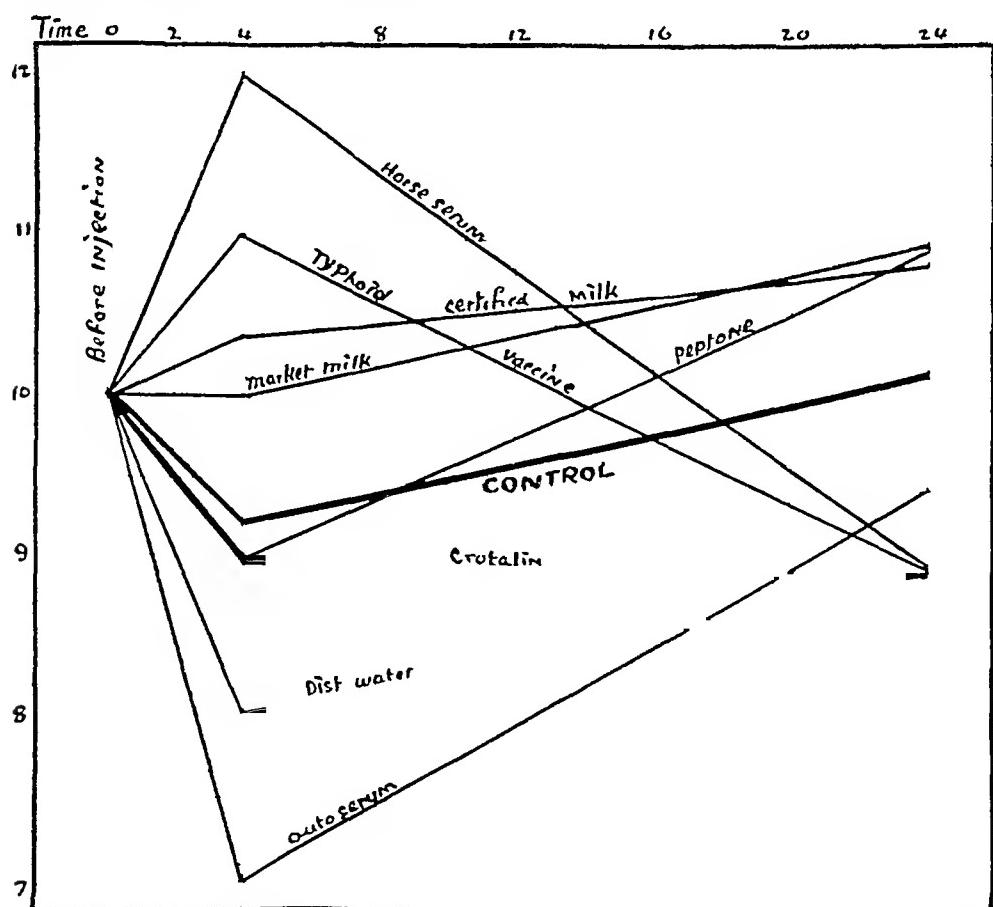


Chart 3—Composite results of influence of various agents on lipolytic enzymes in blood of human being

Influence on Lipolytic Activities—The influence of various agents on lipolytic enzymes was the same as on proteolytic ones as far as their inconsistency and irregularity were concerned. Horse serum and typhoid vaccine induced a quicker lipase response in about four hours after administration, while slower but more persistent increases were found in those inoculated with market milk, certified milk and peptone solution (Table 2 and Chart 3).

CONCLUSIONS

1 Proteolytic, peptolytic and lipolytic serum titers of normal blood are readily influenced by an injection of the following protein agents: distilled water, autoserum, horse serum, certified milk, market milk, crotalins, peptone and typhoid vaccine.

2 A sharp and quick response of proteolytic activity in the serum follows an injection of peptone solution, and of horse serum, while a steady and persistent increase follows an injection of any of the following agents: market milk, distilled water and certified milk, named in the order of their potencies.

3 It seems that there is a steady increase of peptidase titer in the serum, approaching its maximum at about twenty-four hours after an injection of any of the agents used. A decided drop of peptidase titer follows treatment with typhoid vaccine, autoserum and peptone, some time within four hours after treatment.

4 Horse serum and typhoid vaccine produce a sharp and quick response of increased lipolytic serum titer, but market milk, certified milk and peptone produce a steady increase of the serum lipase, persistent for more than twenty-four hours.

5 Bleeding the animal, and the slight trauma resulting therefrom, likewise influence a slight fluctuation of various enzyme contents of the blood.

HOURLY HEMOGLOBIN VARIATIONS IN ANEMIAS *

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The variations that may occur in the percentage of hemoglobin in a normal man during the day have been shown to be considerable¹. As much as 26 per cent has been reported in the course of two hour observations. Numerous factors contribute to this phenomenon.

The question of variations not only in the percentage of hemoglobin but in the color index, red cell volume and plasma cell ratio over two hour periods has been investigated in a series of sixteen cases of anemia. Of these, ten were of the pernicious or addisonian type. The blood was obtained by venipuncture at two hour intervals, beginning at 8 a.m. and terminating at 6 p.m. On each specimen, a red cell enumeration, the hemoglobin percentage by oxygen capacity (Van Slyke) and Dare methods, and plasma cell ratio were determined. From these data, not only the color index and the red cell volume, but also the size of the average cell and the amount of hemoglobin it carried, were readily calculated.

TECHNIC

Collection of Blood—The patients were not restricted as to food or fluids. Eight cubic centimeters of blood was taken, at 8, 10 and 12 a.m., 2, 4 and 6 p.m., by vena puncture. Clotting was prevented by crystals of potassium oxalate. All determinations were carried out by the same person.

Blood Counts—The average of four blood counts was taken. The hemoglobin estimation was made (a) by the oxygen capacity method (Van Slyke), and (b) by a standardized Dare hemoglobinometer. To take the plasma cell ratios, hematocrits were made from glass tubing of equal bore. These, after being filled with blood, were centrifugated for thirty minutes at 3,000 revolutions per minute. The proportion of plasma to cells was accurately measured by a millimeter rule.

Hemoglobin Variations—The largest individual variation of the hemoglobin as estimated by the oxygen capacity method was 11.2 per cent. In two cases it was over 7 per cent, but the average of all sixteen cases was only 5.1 per cent. Taking the secondary anemias alone, it was only 4 per cent. This contrasts with those figures recently pub-

* From the department of metabolism of the Montreal General Hospital.

1 Rabinowitch, I. M., and Strean, G. Hemoglobin Content of Red Blood Cells in Relation to Their Surface Area, *Arch. Int. Med.* 34: 124 (July) 1924.
Rabinowitch, I. M. J. Lab. & Clin. Med. 9: 120 (Nov.) 1923.

lished for the normal men in which two cases showed variations of 26 per cent, and four were between 15 and 20 per cent, the average for the series (twenty cases) being 12.4 per cent. The percentage of hemoglobin, as recorded by the oxygen capacity method, was in all instances higher than that of the Dare. In one case, the maximum variation was plus 20.2 per cent, and in four cases between 15 and 20 per cent. The

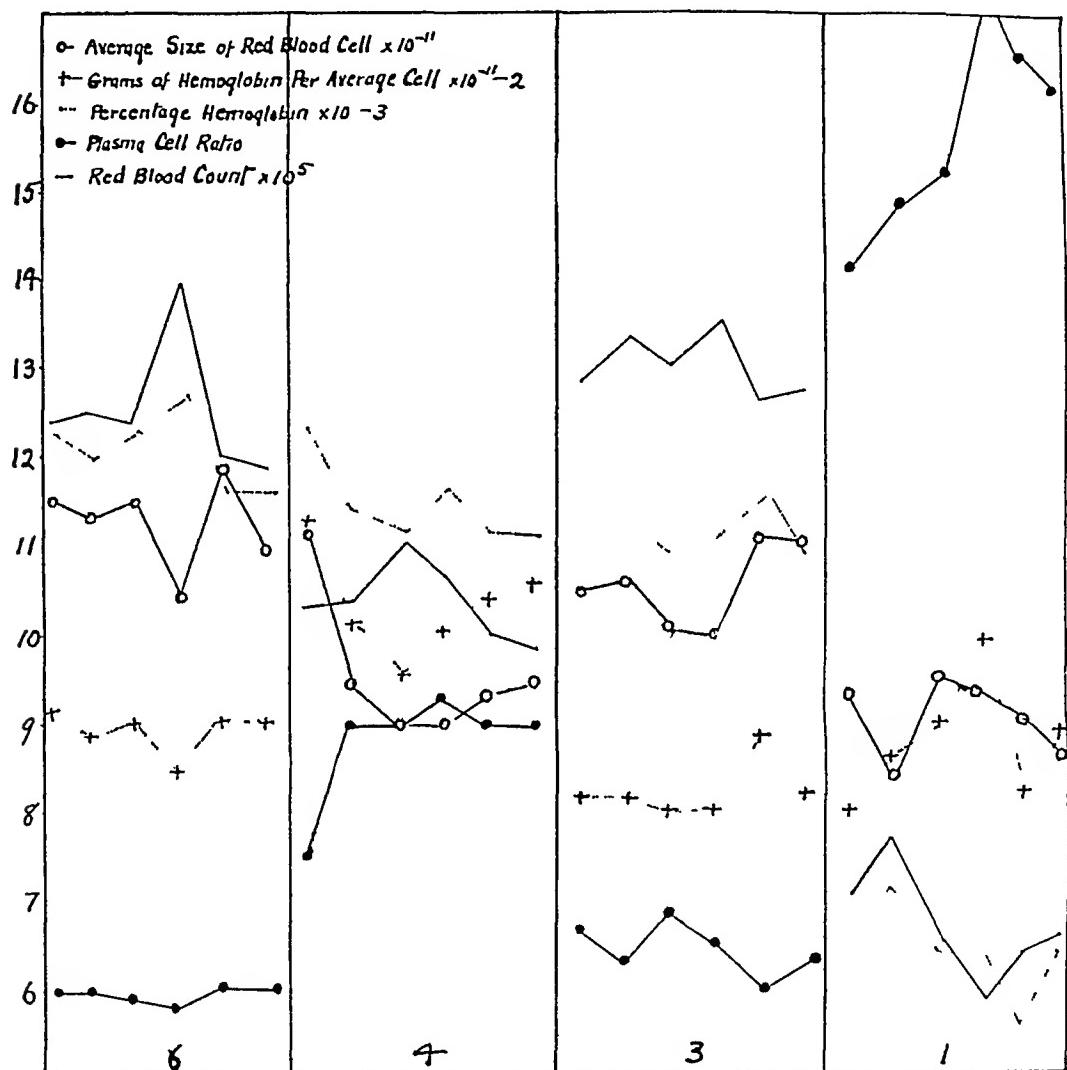


Chart 1

average positive variation for all cases was plus 13 per cent. The Dare hemoglobinometers chosen were of the standardized type used in the medical wards of this hospital.

This discrepancy emphasizes the need for a uniform standard for hemoglobin estimation. The more accurate method of Van Slyke seems to fit in better with the clinical conditions of the patient. The color indexes as calculated by each method also are against the Dare. In Case 1, unquestionably of the pernicious type, the color index would be

only 0.8 by the Dare method, but 1.5 by the Van Slyke method. The same is true of Cases 3, 8 and 10. Table 1 shows a comparison of the indexes as calculated from both methods. Table 2 records the observations made on the hemoglobin, the maximum variations and the average red cell enumeration for each case.

Size and Hemoglobin of Red Blood Cell.—The average size of the red blood cell was obtained by dividing the volume of cells per hundred cubic centimeters of blood (hematocrit) by the number of cells in the same volume (red cell enumeration). The amount of hemoglobin in grams per cell was found by dividing the hemoglobin per hundred

TABLE 1.—Comparison of Indexes as Calculated by Oxygen Capacity and Dare Methods

Case	Red Cell Count	Hemo globin by Oxygen Capacity Method	Gm of Hemo globin per 100 Cc Blood	Index	Index by Dare	Plasma Ratio	Volume of Cells 100 Cc	Volume of Cell $\times 10^{-11}$	Grams of Hemo globin per Cell $\times 10^{-11}$
		Index	Cell Volume			Blood	Cell	Cell	
Pernicious anemia									
1	670,000	21.2	2.97	1.5	0.8	15.4	6.0	9.0	4.4
2	853,000	29.0	4.05	1.6	1.2	9.0	9.2	11.0	4.7
3	1,250,000	37.0	5.18	1.6	0.9	6.4	11.7	10.5	4.1
4	1,046,000	38.4	5.38	1.8	1.2	8.8	9.9	9.5	5.1
5	1,210,000	40.2	5.60	1.6	1.1	6.5	13.1	10.9	4.6
6	1,250,000	40.8	5.64	1.5	1.1	5.0	4.0	11.2	4.4
7	1,260,000	45.4	6.37	1.7	1.4	5.0	16.4	12.9	5.0
8	1,960,000	51.0	7.14	1.2	0.9	4.2	19.3	9.9	3.6
9	1,600,000	59.1	8.27	1.7	1.4	3.6	21.6	13.5	5.1
10	3,060,000	59.4	8.31	0.95	0.7	2.7	27.0	8.8	2.7
Average								10.7	4.4
Secondary anemia									
11	2,780,000	28.7	4.01	0.51	0.3	6.8	12.2	4.5	1.4
12	2,380,000	34.6	4.84	0.72	0.4	6.2	13.5	5.6	2.0
13	2,010,000	39.3	5.50	0.72	0.7	6.5	13.0	6.4	2.6
14	3,690,000	45.8	6.40	0.62	0.5	3.2	24.0	6.4	1.7
15	3,970,000	46.4	6.46	0.58	0.4	3.2	23.5	6.0	1.6
16	3,330,000	57.5	7.20	0.77	0.6	3.2	23.6	7.0	2.1
Average								5.95	1.9

cubic centimeters of blood by the number of cells, as in the former case. The figures, obtained in both the primary and secondary types of anemia, correspond closely with those reported by Haden.² The mean values for the average size of the cell were somewhat smaller, and for the grams of hemoglobin per cell a trifle greater, than those found by the same author. Thus, the average size of the cell in the ten cases of pernicious type was 10.7×10^{-11} . Haden gives the average of twenty cases as 12.8×10^{-11} . The average hemoglobin content of the cell was 4.4×10^{-11} , as compared with 3.75×10^{-11} (Haden) (Table 1).

² Haden, R. L. Acute Criteria for Differentiating Anemias, Arch Int Med 31: 766 (May) 1923.

Hourly Variations in Red Cells—In the more severe grades of anemia dealt with, the numerical values of the red cells showed much less tendency to vary than in the normal case. The greatest variation noted was 501,000, but in only a few instances was it over a quarter million. These were, however, sufficient to account for appreciable differences in the average size of the cell. Thus, in one case, Case 7,

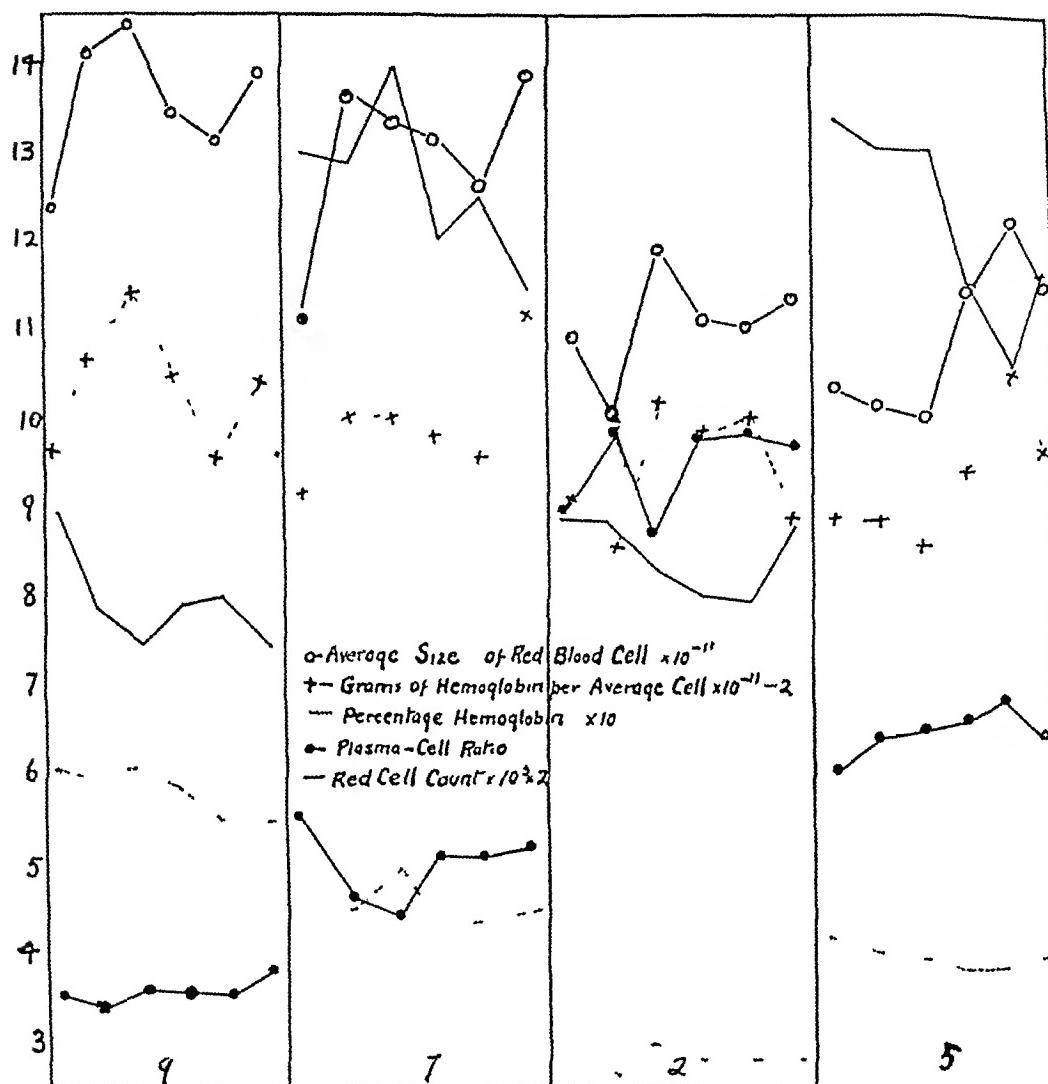


Chart 2

the average size of the cell, as determined at 8 a.m., was 11.1×10^{-11} , while, two hours later, it was 13.6×10^{-11} , or a difference of 2.5×10^{-11} , which means an increase of 18 per cent. The average variations for the primary anemias was 1.69×10^{-11} for the secondary 0.88×10^{-11} . A similar and corresponding variation was noted in the grams of hemoglobin per cell (Table 3). As the average size of the cell increased, the amount of hemoglobin showed a similar rise. This fact is well brought out by the parallelism of the curves of Charts

TABLE 2—*Two Hour Variations in Hemoglobin*

	Oxygen Capacity												Maximum Variation		Diagnosis			
	D ₁ m	D ₂ m	D ₃ m	D ₄ m	D ₅ m	D ₆ m	D ₇ m	D ₈ m	D ₉ m	D ₁₀ m	D ₁₁ m	D ₁₂ m	Oxygen Capacity	Dare Capacity	Dare Capacity	Dare Capacity	Average Blood Count	
1	21.2	10	24.2	14	21.2	10	18.6	11	21.2	11	5.6	4.0	+11.2	670,000	Pernicious anemia			
2	29.9	24	27.4	21	30.7	23	28.7	18	28.7	20	3.3	6.0	+10.7	853,000	Pernicious anemia			
3	36.2	27	37.5	27	36.2	28	37.5	29	38.7	28	3.6	2.5	+10.5	1,250,000	Pernicious anemia			
4	41.2	26	38.0	22	37.5	28	39.2	21	37.5	29	3.7	8.0	+20.2	1,040,000	Pernicious anemia			
5	42.5	30	41.2	30	40.0	20	38.7	28	38.0	28	1.0	2.0	+12.5	1,270,000	Pernicious anemia			
6	41.2	29	40.0	31	41.2	30	42.5	33	38.7	31	3.7	1.0	+12.2	1,250,000	Pernicious anemia			
7	43.2	34	46.2	40	50.0	38	43.2	36	43.7	24	46.2	36	6.8	6.0	+9.2	1,260,000	Pernicious anemia	
8	53.8	40	52.5	36	51.3	42	48.7	35	51.3	38	18.7	30	5.1	7.0	+16.5	1,360,000	Pernicious anemia	
9	61.3	54	60.0	43	61.3	49	59.3	47	56.3	49	56.3	45	5.0	11.0	+17.0	1,600,000	Pernicious anemia	
10	61.3	47	58.8	41	65.0	40	56.3	50	61.3	49	53.8	49	11.2	10.0	+15.0	3,060,000	Pernicious anemia	
11	31.2	23	28.7	19	31.2	23	28.7	20	26.2	18	20.2	21	5.0	5.0	+9.7	2,780,000	Syphilitic anemia ⁴	
12	33.7	26	33.7	25	33.7	23	36.2	24	36.7	21	33.7	23	3.0	5.0	+15.7	2,380,000	Uterine hemorrhage	
13	36.7	28	40.0	29	37.5	28	38.7	29	41.0	29	40.2	27	3.5	2.0	+13.2	2,010,000	Uterine hemorrhage	
14	46.7	44	46.2	43	46.2	47	42.5	46	46.2	38	15.0	39	6.2	8.0	+8.2	3,650,000	Uterine hemorrhage	
15	45.0	38	43.7	38	47.5	36	48.7	11	46.2	36	16.2	37	5.0	11.5	+11.5	3,950,000	Chronic nephritis	
16	46.2	40	47.5	43	53.8	43	53.8	39	53.8	40	7.6	4.0	+11.8	3,350,000	Uterine hemorrhage			
													5.1	5.5				
													+13.0					

Average variation by oxygen capacity method

Average variation by Dare Method

Percentage increase by oxygen capacity over Dare method (average)

1 to 4, representing the factors in question. As was to be expected, the larger the cell, the more hemoglobin it carried. Reduced to unit volume, however, the amount was fairly constant. These figures, in themselves, are of paramount importance only in that they test the accuracy of the red cell enumerations, which, it must be admitted, is the one factor in which the personal equation is liable to enter most

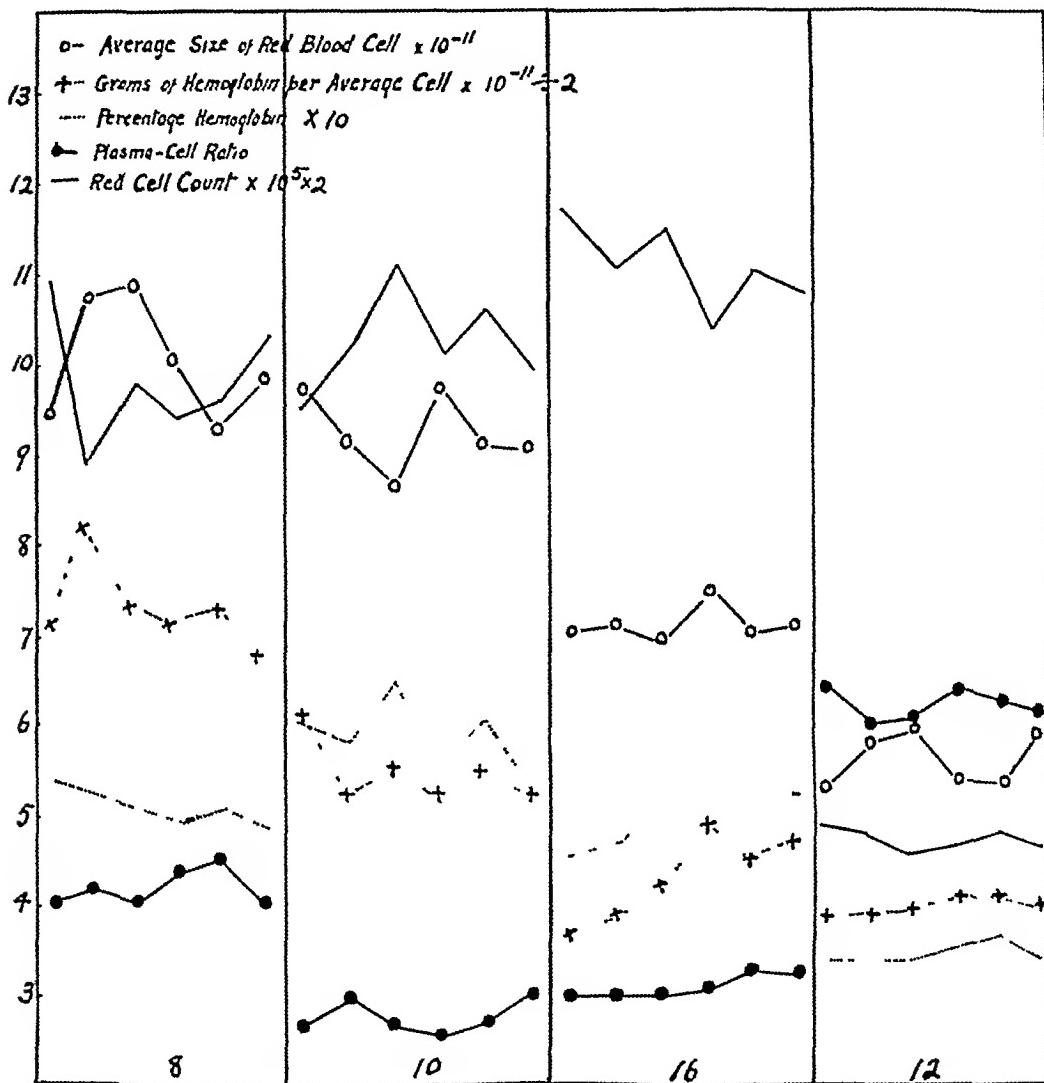


Chart 3

Were the variations artificial, no such parallelism would be obtained, because each curve is dependent on factors other than the red cell count.

RELATION OF HEMOGLOBIN TO CELL SURFACE IN ANEMIA

Former experiments carried out in this laboratory on the non-anemic patients tend to suggest that the hemoglobin is distributed on the surface of the erythrocyte and not, as is usually taught, within the cell itself. They show that, when the total cell volume is constant, varia-

tions in the amount of hemoglobin in that volume, or vice versa, can best be explained by assuming that the hemoglobin is distributed on the surface of the cell. Thus, with an increase in the number of cells (smaller in size), the total volume remaining constant, there results an increased surface area (smaller cells), hence a corresponding increase in the hemoglobin carrying capacity. If this hypothesis is correct, it appears reasonable to assume that it should hold in anemia. A demonstration that such a law either does or does not obtain in cases of anemia would tend to strengthen or negate this hypothesis.

TABLE 3—*Two Hour Variations in Grams of Hemoglobin Per Cell*

	Primary Anemia						Secondary Anemia						Maxi- mum Vari- ation	
	Volume of Red Cell $\times 10^{-11}$						Volume of Red Cell $\times 10^{-11}$							
	8	10	12	2	4	6	8	10	12	2	4	6		
Case a	m	a m	m	p m	p m	p m	Case a	m	a m	m	p m	p m	70	
1	9.3	8.3	9.5	9.3	9.0	8.6	1.2	11	4.6	4.1	4.8	4.7	4.6	
2	10.8	10.0	11.8	11.1	11.0	11.3	1.3	12	5.3	5.8	6.0	5.4	5.9	
3	10.5	10.6	10.1	10.0	11.1	11.0	1.1	13	6.5	6.3	5.5	6.5	6.7	
4	11.2	9.5	9.0	9.0	9.3	9.5	2.2	14	6.2	6.5	6.6	6.0	6.8	
5	10.3	10.2	10.0	11.4	12.2	11.4	2.2	15	6.5	6.2	6.1	6.0	5.8	
6	11.5	11.3	11.5	10.4	11.8	10.9	1.4	16	6.9	7.1	6.9	7.4	6.9	
7	11.1	13.6	13.3	13.2	12.6	13.8	2.7							
8	9.3	10.7	10.8	9.9	9.2	9.7	1.6							
9	12.3	14.1	14.4	13.4	13.2	13.8	2.1							
10	9.6	9.0	8.5	9.6	9.0	9.0	1.1							
Average													0.88	
Primary Anemia							Secondary Anemia							
Grams of Hemoglobin per Cell $\times 10^{-11}$														
Case a	m	a m	m	p m	p m	p m	Case a	m	a m	m	p m	p m	Maxi- mum Vari- ation	
1	4.0	4.3	4.5	5.0	4.1	4.4	1.0	11	1.4	1.3	1.5	1.5	1.3	
2	4.6	4.3	5.1	4.9	5.0	4.4	0.8	12	1.9	1.9	2.0	2.1	2.0	
3	4.1	4.1	4.0	4.0	4.4	4.1	0.4	13	2.7	2.7	2.4	2.7	2.7	
4	5.6	5.1	4.8	5.1	5.2	5.3	0.8	14	1.6	1.7	1.7	1.8	1.7	
5	4.4	4.4	4.3	4.7	5.2	4.8	0.9	15	1.6	1.6	1.6	1.6	1.5	
6	4.6	4.4	4.5	4.2	4.5	4.5	0.4	16	1.8	1.9	2.1	2.4	2.2	
7	4.6	5.0	5.0	4.9	4.8	5.6	1.0							
8	3.5	4.1	3.6	3.5	3.6	3.3	0.8							
9	4.8	5.3	5.7	5.2	4.8	5.2	0.9							
10	3.0	2.6	2.7	2.6	2.7	2.6	0.4							
Average													0.27	

Experiments on cases of anemia showing hourly variations in the number, size and hemoglobin content of the red cell furnish data which, although not convincing in all instances from the point of view of this hypothesis, do support the latter in the same proportion of cases. In support of this conclusion, the graphic evidence in the accompanying charts is presented. In the main, Cases 15, 8, 12, 14, 10 and 1 favor, Cases 9, 7, 2, 6, 5, 3, 4, 11, 13 and 14 present evidence to the contrary. In order to demonstrate that this is so, it is only necessary to consider the curves representing the average size of the red cell and the percentage of hemoglobin. When the average size of the cell increases, it means that per unit volume there is less cell surface, and, if hemoglobin has a surface distribution, then when the curve representing

the average size of the red cell rises, that representing the percentage of hemoglobin should fall. That this does occur is shown by the first group of cases. The others show a reverse condition. It may be seen at a glance that, in the case of the second group, the curve designating the percentage of hemoglobin is roughly parallel to that representing the average size of the cell, and the latter is inversely proportional to the cell surface per unit volume.

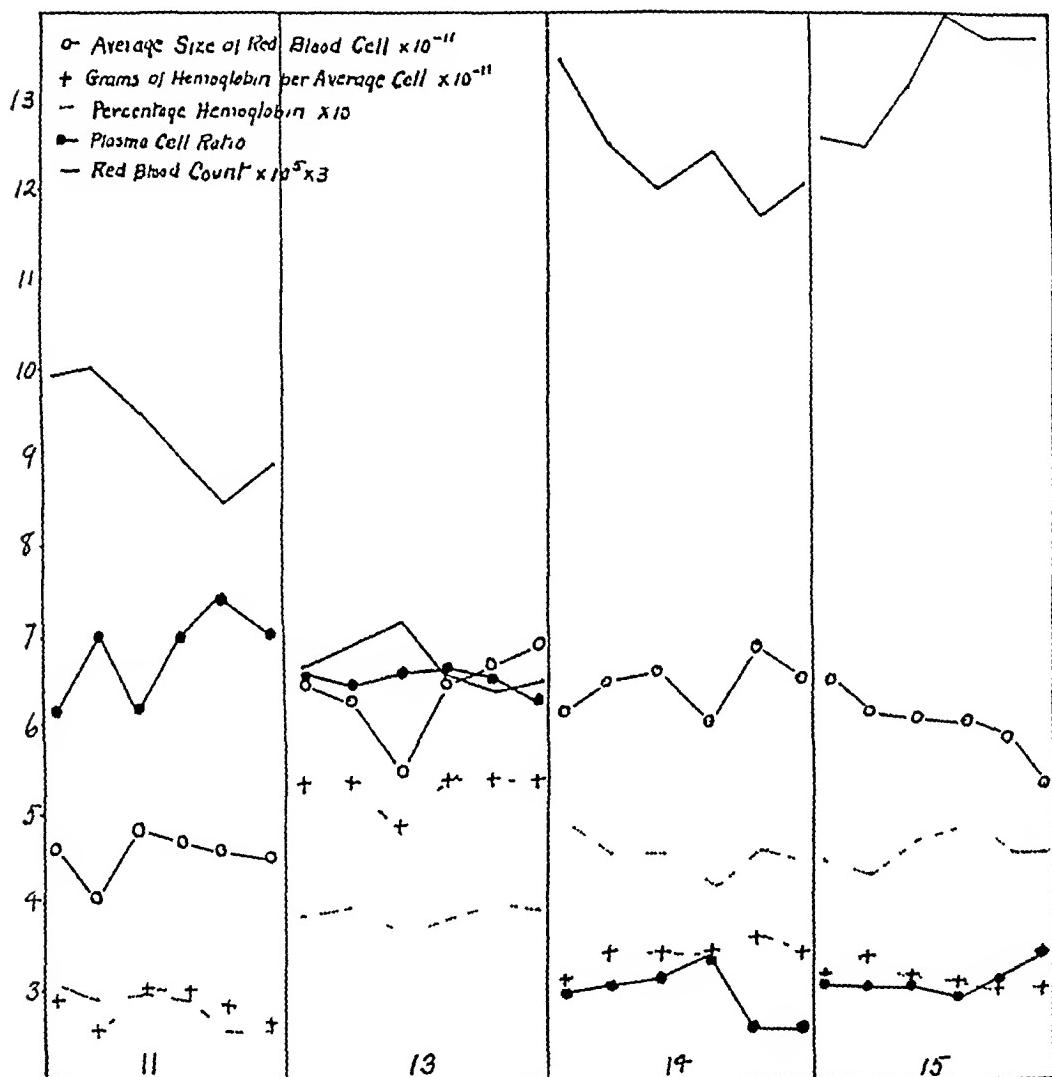


Chart 4

CONCLUSIONS

Hourly variations in the percentage of hemoglobin of the blood, which have been shown to occur in normal persons, do take place in anemia, though to a less extent. Hourly variations in the average size of the erythrocyte may be considerable. A definite relation between the percentage of hemoglobin and the cell surface seems to exist in a certain percentage of the cases.

THE ELECTROCARDIOGRAM AND BLOOD PRESSURE DURING SURGICAL OPERATION AND CONVALESCENCE

OBSERVATIONS ON THIRTY PATIENTS *

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It is apparently the belief of many surgeons and internists that post-operative complications may be lessened or prevented by the preoperative administration of digitalis, even to patients whose hearts are apparently normal¹. The present investigation was undertaken in an attempt to determine the influence of digitalis on certain objective factors during and after surgical operation, but, as no similar study has been found in previous reports, it seemed necessary to establish first a control group of nondigitalized patients for subsequent comparison with a similar group of patients who had received digitalis. It is the nondigitalized group which forms the basis for the present report, the influence of digitalis is discussed in the following paper.

METHOD OF STUDY

It has been our purpose to secure records of the blood pressure and electrocardiograms at frequent intervals during the induction of anesthesia and operation, and records of the blood pressure and clinical course during ten or more days of convalescence. There was no selection of patients on the basis of age, sex or cardiac condition, but an effort was made to secure a wide variety of the more serious operative conditions. The preoperative blood pressure was obtained, in most instances, at least twenty-four hours before operation, and patients with auricular fibrillation or hypertension had several readings taken, in order that the usual range of variation might be determined. The subjects were connected with the electrocardiograph and the blood pressure manometer in the anesthesia room before the anesthetic was started, and preliminary records were secured. One observer remained in the operating room from the beginning of anesthesia until the end of the operation to determine the blood pressures and to signal for electrocardiograms. He was seated within several feet of the patient so that the effect of trauma, traction on the viscera, hemorrhage and depth of

* From the Department of Internal Medicine, Yale University School of Medicine, and the New Haven Hospital

¹ References may be found in Marvin, H M , Pastor, R B , and Carmichael, M Effect of Routine Preoperative Digitalization on the Electrocardiogram and Blood Pressure During Surgical Operation and Convalescence, Arch Int Med , this issue

anesthesia could be noted. There was constant connection with the electrocardiographic laboratory through a special telephone and electric buzzer.

As a general rule, the blood pressure was determined every two and a half minutes, and at every second or third determination an electrocardiogram was taken simultaneously in response to a signal. Observations were made more frequently if unusual circumstances arose, and it was always possible to determine whether changes in blood pressure or heart rate were dependent on a new cardiac mechanism or some other factor. Most electrocardiograms were of Lead II, but all three leads were taken at the beginning, at intervals during, and at the conclusion of, the operation. About 750 records were secured from the thirty patients who were studied.

Postoperative observations began approximately six hours after the conclusion of the operation, and were made three times a day for the first four days, twice a day for the next four days, then once a day until the patient was discharged or convalescence was well established. These observations included the determination of the systolic and diastolic pressures and careful notes as to the occurrence of nausea and vomiting, the rapidity of convalescence, the presence of complications, and the general clinical condition of the patient. The total number of blood pressure readings, including those secured during operations, was more than 2,400, an average of about eighty for each patient. Electrocardiograms were taken during convalescence only when there was some indication for them.

The sphygmomanometers used were of the standard mercury type; the same two instruments were used throughout the study. All determinations as well as all clinical notes, were made by the authors, whose readings corresponded accurately. The fourth phase was taken as the diastolic pressure in all cases, and in patients with auricular fibrillation the maximal beats were taken as the systolic pressure. Thirty patients were studied.

BLOOD PRESSURE DURING OPERATION

It is notoriously difficult to draw satisfactory conclusions as to the cause of moderate changes in blood pressure because of the multiplicity of factors involved, many of them but little understood. It has seemed advisable to classify our results only in a general way, and the cases have been arbitrarily arranged in four groups: (a) Those in whom the blood pressure rose during the induction of anesthesia and remained above the preoperative level during the entire operation, (b) those in whom the blood pressure, after a preliminary rise, fell and remained below the preoperative level throughout the operation, (c) those in whom the pressure fluctuated within wide limits, both above and below the preoperative blood pressure, and (d) those in whom the blood pressure,

during operation, remained at the preoperative level. This same classification has been applied to the postoperative blood pressures obtained after the first day, but those obtained at the end of six, eighteen, twenty-four and thirty hours after operation have been listed separately for the sake of more accurate comparison with our digitalized patients and with the observations of other authors.

It should be noted that, in this classification, blood pressures have been considered "above" or "below" the preoperative pressure only when the difference between them was greater than 4 mm of mercury. If the two pressures differed by 4 mm or less, it was considered that there had been no change. We believe this difference to lie within the limit of error of observation.

Almost without exception, there was a rise in both systolic and diastolic pressures during the induction of general anesthesia; this has been noted so often as to need no discussion. If this elevation proved transient, as in many cases, it was disregarded for purposes of classification. It also was noted that the blood pressure in many patients rose and fell directly with the depth of anesthesia, and that there was almost always less fluctuation in pressure if the anesthesia was fairly deep. The operative procedure itself seemed to have no influence on the blood pressure unless it involved obstruction to the respiration (operations on the throat and jaw) or was continued for four or five hours. It was possible often to confirm the statement of Miller² that "the most severe surgical manipulations may regularly be performed without marked change in either the blood pressure or the pulse rate." In a few patients, posture seemed to be responsible for changes in pressure, a change to the Trendelenburg position was occasionally followed promptly by a fall in blood pressure which was corrected when the table was again lowered; in a very few, a steadily falling blood pressure was apparently stopped from further depression by lowering the head of the table.

Apart from these general considerations, it is of interest to observe the relation of the operative to the preoperative blood pressures in the present series. One patient has been omitted because, at the time of admission to the accident room, the systolic pressure was so low as to be unobtainable. Of the remaining twenty-nine, the blood pressure during operation was constantly above the preoperative level in thirteen, constantly below in thirteen, fluctuating above and below in two, and the same in one. The distribution of these groups with regard to the type of anesthesia is shown in Table 1.

Five patients developed "surgical shock" during operation. In all of them the steady fall in blood pressure was the first indication of danger,

² Miller, A. H. Blood Pressure Guides During Anesthesia and Operation, Am J Surg (Anesthesia Supplement) 35:34 (April) 1921.

and in two of them it preceded other evidences by a considerable period of time

BLOOD PRESSURE DURING THE THIRTY HOURS AFTER
OPERATION

The figures obtained during the first thirty hours following operation are perhaps of the greatest interest Geist and Somberg³ and Geist and Goldberger⁴ have laid great emphasis on a postoperative fall in blood pressure as an apparent cause of postoperative complications. Their observations in thirty-nine patients showed an average fall in blood pressure of 14 mm at six, twelve and twenty-four hours after operation. They quote Polak⁵ as also having shown an average fall of 14.2 mm in the blood pressure after operation, but Polak's readings were made only one hour after the conclusion of the operation, and apply only to etherized patients. Lehrnbecher⁶ feels that the blood pressures immediately after operation is of little importance, but that those obtained in the evening and on the morning following are of considerable aid in prognosis.

TABLE 1.—*Blood Pressures During Operation in Twenty-Nine Cases**

Anesthesia	Above	Below	Same	Fluctuating
Gas oxygen (nitrous oxide)	6	8	1	1
Ether	2	4		
Procain	4	1		
None	1			1

* As compared with the preoperative blood pressure

The figures obtained in the present study fail to show a fall in the systolic blood pressure after operation in the majority of cases. The records of four patients, Cases 16, 25, 28 and 30, were not included in the following analysis, one of them because the preoperative blood pressure could not be obtained, and the other three because they were in a condition of shock at the end of operation, and the blood pressure rose slowly throughout the following day. Of the remaining twenty-six, there were only eight (31 per cent) whose blood pressure at the end of six hours was lower than the preoperative pressure, while at the end

3 Geist, S. H., and Somberg, J. S. Preoperative Digitalization. A Method to Reduce Postoperative Complications, Am J Obst & Gynec 4 135 (Aug) 1922

4 Geist, S. H., and Goldberger, M. A. Effect of Preoperative Digitalization in Reducing Postoperative Complications, Ann Surg 78 693 (Dec) 1923

5 Polak, J. O. A Clinical Study in Preoperative and Postoperative Blood Pressures and Their Relation to Renal Function and in Shock and Hemorrhage, Am J Obst 80 113 (Aug) 1919

6 Lehrnbecher, A. Die theoretische Grundlage und praktische Anwendung der Blutdruckmessung bei chirurgischen Eingriffen, Beitr z klin Chir 127 291, 1922

of eighteen hours the pressure had returned to or above the preoperative level in all except five (19 per cent).

If the figures are analyzed with regard to the relation of the postoperative pulse pressure to the preoperative pulse pressure, the results are slightly different but they point to a similar conclusion that the great majority of the patients during the thirty hours following operation have pulse pressures as great as, or greater than, before operation. The number of patients who showed changes in the systolic and pulse pressures at intervals after operation is shown in Table 2.

The eight patients who showed a transient fall in blood pressure after operation (Cases 3, 12, 13, 20, 21, 22, 23 and 24) all had uneventful recoveries.

GENERAL POSTOPERATIVE BLOOD PRESSURES

Under the term "general postoperative blood pressures," we have classified all those obtained after the first thirty hours following operation, the readings begin, therefore, with the morning of the second day. The figures obtained for each patient have been charted and the relation

TABLE 2—*Blood Pressures During the Thirty Hours After Operation**

	Systolic Pressure			Pulse Pressure		
	Above	Below	Same	Above	Below	Same
6 hours after operation	11	8	7	8	9	9
18 hours after operation	14	5	7	10	8	8
24 hours after operation	13	6	6	6	8	11
30 hours after operation	11	3	10	7	4	13

* As compared with the preoperative systolic and pulse pressures.

of the curve to the preoperative level established. Sharp deviations of the blood pressure above or below the general level which were noted at only one observation have been disregarded for purposes of classification. Two patients died within three days after operation, of the remaining twenty-eight whose courses were followed for periods of from eight to twenty days after operation, the blood pressure was constantly above the preoperative level in nine, constantly below in twelve, and the same in seven.

COMPLICATIONS

There were postoperative complications in four patients, all of whom developed bronchopneumonia, one of them had erysipelas also. Signs of pneumonia were detected in two patients on the second day after operation, in one on the third, and in one on the sixth. In two instances (Cases 25 and 26), it followed operations on the jaw and pharynx which were attended by severe trauma and undoubtedly inhalation of blood and mucus, in the other two (Cases 7 and 10), it occurred after upper abdominal operations in patients whose anesthetization was marked by unusual struggling and vomiting. For the purpose of this study, it is

TABLE 3—*Blood Pressures in Nondigitalized Cases*¹

Case	Age	Operation	Length of Operation	Preoperative Blood Pressure				Postoperative Blood Pressure				General Post-operative Blood Pressure			
				Anesthesia		General Operative Blood Pressure		6 Hr		18 Hr		24 Hr		30 Hr	
				Sys	Dia-	Sys	Dia-	Sys	Dia-	Sys	Dia-	Sys	Dia-	Sys	Dia-
1	54	Cervical symp- tectomy	2 Hr 10 Min	Local	78	Above	130	82	140	80	136	76	Above	Arteriosclerotic heart disease, anginal failure	
2	48	Cervical symp- tectomy	2 Hr 16 Min	Local, gas oxygen	60	Fluctu- ating	126	60	132	58	132	60	Above	Syphilitic heart disease ^c , aortic insufficiency and anginal failure	
3	38	Exploratory	1 Hr 43 Min	Gas oxygen	110	68	Above	100	70	110	84	100	90	Below	Gumma of liver, excellent recovery
4	63	Colostomy	1 Hr 40 Min	Gas oxygen	98	48	Above	98	58	110	68	112	70	Below	Carcinoma, rectum
5	42	Resection, sigmoid	2 Hr 22 Min	Gas oxygen	112	82	Above	154	90	154	92	156	94	Below	Fluctuating
6	40	Resection, colon	45 Hr 22 Min	None	90	Above	152	90	168	92	168	94	Below	Acute delirium, bronchopneumonia	
7	38	Perforated gastric ulcer	1 Hr 22 Min	Ether	70	Below	110	70	120	80	120	80	Below	Fluctuating	
8	38	Gastro enterostomy	2 Hr 22 Min	Local, gas oxygen	130	38	Above	138	36	134	40	132	38	Below	Syphilitic heart disease, aortic insufficiency
9	67	Resection, stomach	3 Hr 30 Min	Gas oxygen	94	70	Fluctuating	128	70	124	70	128	72	Below	Postoperative bronchopneumonia and croup
10	28	Cholecystectomy	1 Hr 30 Min	Gas oxygen	126	78	Above	130	86	124	95	124	88	Below	Postoperative bronchopneumonia and croup
11	26	Cholecystectomy	2 Hr 18 Min	Gas oxygen	118	70	Below	145	100	142	88	142	94	Below	Fluctuating
12	16	Nephrectomy	2 Hr 30 Min	Gas oxygen	106	92	Steady fall	146	92	172	94	168	98	Below	Excellent recovery
13	23	Ligation, superior thyroid artery	30 Hr 41 Min	Gas oxygen	160	84	Below	154	82	146	76	148	78	Below	Thyrotoxosis, excellent recovery
14	23	Thyroidectomy	50 Hr 52 Min	Local	160	80	Above	180	96	184	98	180	98	Below	Thyrotoxosis
15	26	Cardiomyosis	1 Hr 46 Min	Local	98	52	Below	100	60	100	58	102	60	Below	Rheumatic heart disease, adhesive pericarditis
16	14	Pericardiotomy	1 Hr 15 Min	Ether	45	?	Not taken	114	70	110	60	110	70	Below	Stab wound of heart
17	74	Amputation of leg	1 Hr 15 Min	Gas oxygen	120	82	Above	130	78	128	76	138	74	Below	Arteriosclerotic heart disease, auricular fibrillation
18	9	Open reduction, tibia	1 Hr 55 Min	Ether	110	80	Above	108	70	110	80	108	78	Below	Fluctuating
19	61	Cystotomy	1 Hr 52 Min	Gas oxygen	120	72	Above	118	72	120	70	118	72	Below	Excellent recovery
20	56	Prostatectomy	1 Hr 48 Min	Gas oxygen	145	80	Below	140	86	130	71	134	78	Below	Excellent recovery
21	22	Hysterectomy	1 Hr 15 Min	Gas oxygen	118	66	Below	92	58	140	90	126	72	Below	Shock from hemorrhage, excellent recovery
22	47	Panhysterectomy	2 Hr 45 Min	Gas oxygen	154	80	Below	112	84	128	94	142	92	Below	Excellent recovery
23	37	Cesarean section	1 Hr 20 Min	Gas oxygen	162	90	Below	128	84	120	82	122	80	Below	Rheumatic heart disease, excellent recovery
24	23	Hystrectomy	2 Hr 48 Min	Gas oxygen	140	82	Below	132	80	130	82	128	84	Below	Marked trauma, died of pneumonia
25	56	Carcinoma, jaw and neck	3 Hr 48 Min	Ether	98	60	Steady fall	*	90	50	92	60	90	54	Below
26	74	Carcinoma, jaw	3 Hr 15 Min	Local, chloro- form	118	68	Above	142	70	155	78	160	76	Below	Marked trauma, died of pneumonia
27	39	Bilateral hemothorax	2 Hr 10 Min	Gas oxygen	124	84	Same	122	82	126	88	126	82	Below	Shock
28	56	Bilateral breast cancer	3 Hr 12 Min	Ether	236	110	Steady fall	142	70	216	132	204	112	Below	Shock
29	45	Decompression	2 Hr 12 Min	Ether	106	74	Above	124	90	132	90	124	90	Below	Marked trauma, died of pneumonia
30	45	Glioma of brain	5 Hr 12 Min	Ether	120	88	Steady fall	82	58	110	78	133	84	Below	Shock

* Blood pressure too low to be obtained.

important to observe that, in three of these four patients, the blood pressure, during the thirty hours following operation, was at or above the preoperative level, while in the fourth, a patient who left the table in profound shock, the pressure rose subsequently almost to the level noted before operation. Our findings, in this respect, differ from those of Geist and his collaborators, who observed pulmonary complications only in those patients who had shown a postoperative fall in blood pressure.

A summary of the thirty cases, with blood pressure changes during and after operation, is given in Table 3.

ELECTROCARDIOGRAPHIC STUDIES

We have found only three references to the study of electrocardiograms taken during or immediately following surgical operations. In 1918, Heard and Strauss⁷ reported an instance of atrioventricular rhythm occurring in a patient still under the influence of ether following operation. Levine⁸ later reported two cases of paroxysmal auricular tachycardia detected by means of electrocardiograms in patients who had been operated on and were still under ether. The only comprehensive study appears to be that of Lennox, Graves and Levine,⁹ who secured frequent records from fifty patients during operation. These observers state in conclusion:

About one half of the cases showed some abnormality of the mechanism of the heart beat not present in preliminary tracings, the most prominent being paroxysmal auricular tachycardia, premature beats, and marked displacement of the cardiac pacemaker. The observed abnormalities of the heart beat were transient and unassociated with clinical signs of embarrassed circulation. In the main, they were of physiological rather than of clinical significance.

There is a striking similarity between the findings in our patients and those of the authors just quoted, as regards the percentage and character of electrocardiographic changes. Fifteen of our thirty cases (50 per cent) showed some definite abnormality during operation which was not present in preliminary tracings. Sino-auricular, or physiologic tachycardia has not been regarded as abnormal, although several patients maintained a rate distinctly above normal throughout operation. The observed changes are discussed below.

⁷ Heard, J. D., and Strauss, A. E. An Electrocardiographic Study of Two Cases of Nodal Rhythm Exhibiting R-P Intervals, *Am J M Sc* **75** 238, 1918.

⁸ Levine, S. A. Acute Cardiac Upsets Occurring During or Following Surgical Operations, *J A M A* **75** 796 (Sept 18) 1920.

⁹ Lennox, W. G., Graves, R. C., and Levine, S. A. An Electrocardiographic Study of Fifty Patients During Operation, *Arch Int Med* **30** 57 (July) 1922.

SINUS ARRHYTHMIA AND BRADYCARDIA

Only one patient exhibited sinus arrhythmia, she was likewise the only one in whom bradycardia was noted almost constantly. She was 54 years of age, and was considered to have definite arteriosclerotic heart disease with angina pectoris. The operation was resection of the left cervical sympathetic nerve, with removal of the superior cervical ganglion, it was performed under procain anesthesia. The vagus and sympathetic trunks lay unusually near each other in this patient, and there was considerable vagal stimulation, some of it deliberate. It is quite possible that the arrhythmia may have been a vagal effect.

PREMATURE BEATS

Premature beats were registered in seven patients, none of whom had shown such beats in the preliminary tracings or during physical

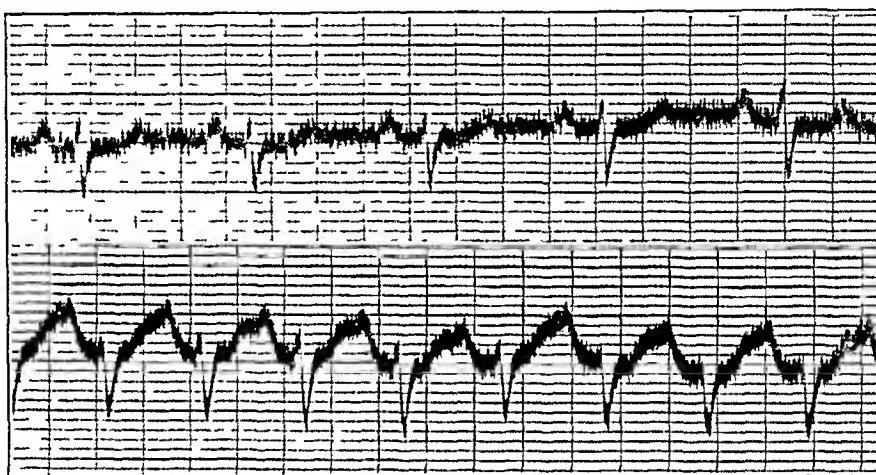


Fig 1 (Case 26)—Lead II above, normal mechanism with rate of 80 a minute, below, paroxysmal tachycardia with rate of 142 a minute. In this and the following electrocardiograms, distances between abscissas represent 10^{-4} volts, and time is in one-fifth seconds.

examination. In six of them, the ectopic beats arose in the ventricles, in the seventh, the origin was in the junctional tissues. Two of these patients were elderly, with peripheral arteriosclerosis and evidences of arteriosclerotic heart disease, one of them had also auricular fibrillation. No abnormality of the cardiovascular system was detected in the remaining five. The premature beats occurred with greater frequency during the induction of anesthesia or the early part of the operation, but in three patients they were recorded at intervals throughout the operation.

INCREASE IN SIZE OF T WAVE

In one patient there was a remarkable increase in the amplitude of the T wave in Lead II during the early part of the operation. This

wave, which was upright at all times, became approximately twice as high as normal without alterations in any other deflections. It returned to its previous size before the operation had been finished.

PAROXYSMAL TACHYCARDIA

There were two instances of paroxysmal tachycardia, in one patient the arrhythmia was noted in only one record, but, in the other, the paroxysms occurred throughout the period of operation. They were unaccompanied by signs of circulatory embarrassment. It is of some interest to note that both these patients received ether through a nasal tube introduced into the pharynx. The electrocardiograms of Case 26 are shown in Figure 1.

A third patient during operation showed short runs of ventricular premature beats which might strictly be interpreted as paroxysms of ventricular tachycardia, but these occurred at a time when the heart was being handled by the surgeon, who was removing blood from the peri-

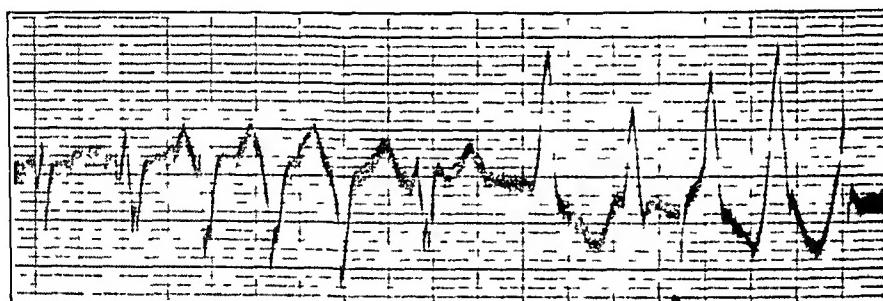


Fig 2 (Case 16) —Lead II series of ectopic ventricular beats which occurred during handling of heart, first complex in record is a normal one with the T wave slightly distorted.

cardial sac. While the mechanical stimulation of the heart was doubtless responsible for the series of ectopic beats, illustrated in Figure 2, isolated premature beats were registered before the pericardium was opened, so the case has been listed with that group.

DISPLACEMENT OF THE PACEMAKER

The most frequent abnormality in our records was a conspicuous change in the P wave, which occurred in seven patients (23 per cent). This is in accord with the observations of Lennox, Graves and Levine, who found such changes in 30 per cent of their patients during operation. In the present study, the changes were of only two types (1) a complete disappearance of the P wave, which apparently became buried in the Q-R-S complex, and (2) the appearance of an inverted P wave following the Q-R-S complex. Seven patients showed the first type, one of them in addition showed the second.

It seems fairly clear that a majority, if not all, of such changes represent a displacement of the pacemaker downward, usually into the auriculoventricular node, but Levine⁹ has clearly pointed out the difficulties which lie in the way of that assumption, and has emphasized the lack of agreement as to the criteria by which auriculoventricular rhythm is to be diagnosed from electrocardiograms. We have followed his

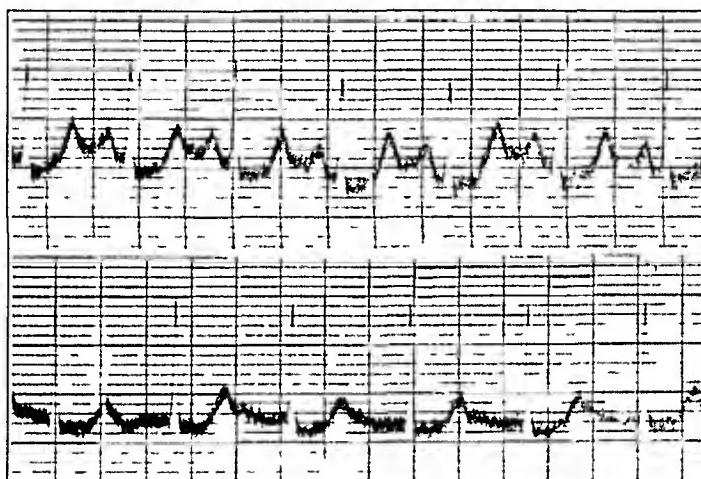


Fig 3 (Case 21)—Lead II above, normal mechanism, below, displacement of pacemaker. Absence of P waves in lower record should be noted.

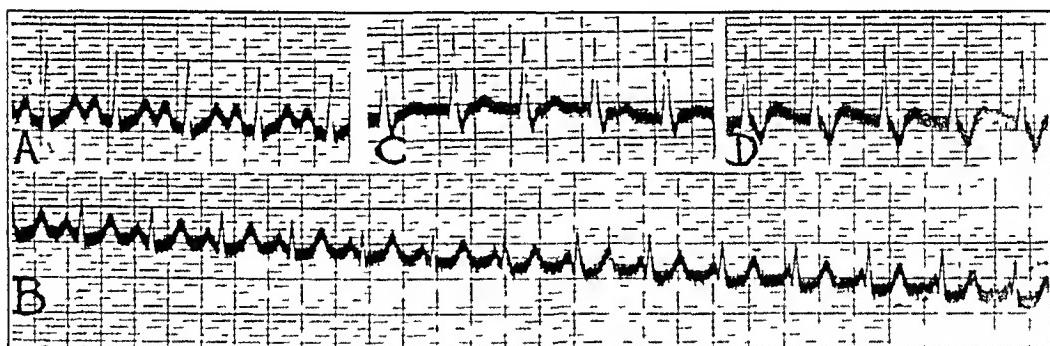


Fig 4.—A, Lead II, normal mechanism, B, Lead III, taken a few seconds later, showing the gradual merging of the P Wave with the Q-R-S group, C and D, Lead II taken at intervals of about three minutes, showing different types of displacement of the pacemaker. A and B were made before induction of anesthesia, C and D during induction.

example in referring to this group as simply "displacement" of the pacemaker. Figure 3 shows the change which characterized the record of six patients; they were so uniform that only one has been reproduced. In Figure 4, there is clearly shown the two different mechanisms which controlled the heart in Case 23. The portion of this figure labelled B was taken a few seconds after A, and shows the gradual shortening of the P-R interval until the P wave is lost in the Q-R-S group. About

three minutes elapsed before *C* was taken, and an equal interval between *C* and *D*, both of which are of Lead II. In the former of these, no P waves are visible, in the latter, the inverted waves immediately following the Q-R-S complex are thought to be retrograde auricular waves. Every tracing secured during operation from this patient showed the mechanism illustrated in *C* or *D*, but an electrocardiogram taken several days later showed normal mechanism.

It should be pointed out that the displacement of the pacemaker in this case occurred before anesthesia had been started, the first two records in Figure 4 were taken while the patient was in the anesthesia room awaiting the arrival of the surgeon. This was the only instance in which a transient abnormality was noted in the preliminary tracings, but it affords further evidence of the ease with which the pacemaker may be disturbed. The presence of rheumatic heart disease with mitral stenosis and insufficiency may have had some bearing on the early appearance and long duration of the arrhythmia in this case.

No one factor has been discovered which might be of importance in causing this change in the electrocardiogram. Of the patients manifesting it about half were below the age of 40, and half above, the sexes were almost equally represented, the changes occurred with both ether and nitrous oxid-oxygen anesthesia, and the operations involved such diverse parts of the body as the uterus, stomach, jaw and brain. The length of anesthesia varied from one hour and fifteen minutes to slightly more than five hours, but in no instance did a displacement of the pacemaker occur during the latter part of a long operation.

RELATION OF ELECTROCARDIOGRAPHIC CHANGES TO BLOOD PRESSURE

The determination of the blood pressure simultaneously with the registration of the electrocardiogram has afforded an opportunity to study a possible relation between disturbed cardiac mechanism and changes in blood pressure. We have failed to establish any such relation. In several cases, there seemed to be a simultaneous change in blood pressure and electrocardiogram, but, in every instance, the change in pressure was maintained, while the electrocardiographic change was transient. In many cases, the arrhythmia recurred, and in none was the blood pressure the same during the successive episodes.

A summary of the changes in blood pressure associated with variations in the electrocardiogram is given in Table 4. When two blood pressures are given, they represent the readings taken simultaneously with the first and last electrocardiograms that displayed the abnormal mechanism.

TABLE 4.—*Electrocardiograms and Blood Pressures*

Case	Age	Cardiac Diagnosis	Preoperative Blood Pressure		Abnormalities In Electrocardiograms	Simultaneous Blood Pressure		Remarks
			Sys. tolie	Dias. tolie		Sys. tolie	Dias. tolie	
1	54	Arteriosclerotic heart disease with anginal failure	130	78	Sinus arrhythmia and bradycardia Junctional premature beats	156	84	Pulse slowed when working near vagus nerve
3	38	Normal	110	68	Displacement of pace- maker Ventricular premature beats	126	80	
4	63	Normal	98	48	Ventricular premature beats	140	88	
8	38	Syphilitic heart dis- ease, aortic insufficiency	130	38	Increase in size of T wave in Lead II	160	84	
10	28	Normal	126	78	Displacement of pace- maker	142	86	
16	14	Stab wound of heart	45	?	Ectopic ventricular beats isolated and in short paroxysms	Unob- tainable		Heart handled during parox- ysms
17	74	Arteriosclerotic heart disease auricular fibrillation	120	82	Ectopic ventricular beats	140	96	
20	56	Normal	145	80	Displacement of pace- maker	170	106	
21	22	Normal	118	68	Displacement of pace- maker	100	72	Shock from hem- orrhage
22	47	Normal	154	80	Ventricular premature beats	188	104	
23	37	Rheumatic heart dis- ease	132	90	Displacement of pace- maker	152	90	Onset of auriculo- ventricular rhythm before anesthesia
25	56	Normal	98	60	Displacement of pace- maker	134	74	Marked trauma, shock
26	74	Normal	118	68	Paroxysmal tachy- cardia Ventricular premature beats	178	90	
30	45	Normal	120	88	Displacement of pace- maker Paroxysmal junctional tachycardia	104	78	Shock
						144	88	
						180	112	

RELATION OF CHANGES TO CARDIAC PATHOLOGY

Six patients in this series had definite signs of heart disease. In two of them, the etiology was rheumatic infection, in two it was syphilitic, and in two the changes were apparently arteriosclerotic in origin. Anginal heart failure was present in two patients, but none showed evidences of congestive failure. From the standpoint of blood pressure changes and clinical course, these patients withstood operation as well as any normal individual. Four of them, it is true, showed electrocardiographic changes during operation, but in one they were probably due to direct vagal stimulation. If that minor change be disregarded, the percentage of electrocardiographic changes in the cardiac patients becomes practically the same as that in normal persons.

SIGNIFICANCE OF ELECTROCARDIOGRAPHIC CHANGES

Of the four patients who developed surgical shock, three showed a displacement of the pacemaker in electrocardiograms. But in these three

the electrocardiographic change was transient and had disappeared long before signs of shock appeared, in all of them, moreover, there was an adequate apparent cause for the shock quite apart from a minor change in the cardiac mechanism. In one, there was profuse hemorrhage, in another, the operation on the brain lasted five hours, and in the third there was prolonged and extensive cauterization of the jaw, neck and pharynx in a patient whose anesthetization was difficult and very unsatisfactory. In none of the other patients was there any evidence that the abnormalities in the electrocardiogram had a clinical significance, either at the time of their occurrence or afterward.

COMMENT

On many occasions during this study, patients had the blood pressure determined as often as once a minute for considerable periods of time, and almost without exception readings were taken every two and a half minutes. These frequent observations have shown that the pressure may fluctuate within wide limits above and below its usual level without other apparent change in the circulation or general condition of the patient. In this study, the only change which has seemed of significance has been the steady and conspicuous fall in pressure which accompanied the appearance of surgical shock. Rises in pressure as great as 100 mm above the preoperative level have been unassociated with signs of circulatory disturbance, and significant lowering (amounting to half the systolic pressure in hypertensive individuals) has likewise been without clinical manifestations unless it reached levels of from 80 to 90 mm of mercury. The rarity or frequency of fluctuations in the blood pressure level has had no apparent significance, and it appears certain that the behavior of the blood pressure during operation has afforded no indication of its subsequent behavior or of the clinical course of the patient. The changes in the electrocardiogram during operation were largely of a minor character, and had no demonstrable influence on the circulation so far as could be determined by blood pressure readings and clinical observations. We are in complete agreement with those previous observers who considered them of physiologic interest rather than of clinical importance.

With regard to determinations of the blood pressure after operation, it may be said that they have been of no value whatever in estimating the danger of postoperative complications or the type and duration of convalescence. This statement does not apply to those patients who left the operating table in shock, in whom, frequent observation of the blood pressure seemed essential. Attention has already been directed to the fact that very few of the patients in the present series showed a post-operative fall in pressure, and that convalescence in those few was uneventful. A careful comparison of clinical notes and blood pressure

records obtained during the ten days following operation fails to disclose any constant relation between them, except that during the later days of convalescence many patients had a pressure lower than before operation. That this moderate fall may be attributed largely to prolonged rest in bed is indicated by similar findings in many other medical and surgical patients who were not subjected to anesthesia and operation.

The four patients who developed postoperative complications did not have a postoperative lowering of the blood pressure, or any other changes which were distinctive.

SUMMARY

The blood pressure has been determined, and electrocardiograms taken, at frequent intervals during anesthesia and operation in thirty patients. Blood pressures were determined and clinical notes made at regular intervals each day for ten or more days of convalescence.

The blood pressure during operation varied considerably, it was constantly above and constantly below the preoperative level in an equal number of cases. Changes in pressure in either direction seemed to be without clinical significance except when there was extreme lowering of the systolic and pulse pressures in cases of shock.

The majority of patients, in this series, failed to show the postoperative fall in systolic and pulse pressures reported by some observers and assumed by many. Of the few patients who did show such a fall, none developed postoperative complications or had a protracted convalescence.

Blood pressures during the first thirty hours after operation, as well as those taken during the following ten days, were found to be of no value in estimating the likelihood of complications or the rapidity of convalescence.

Electrocardiograms taken during operation showed definite changes, not present in preliminary tracings, in about half the cases. The chief of these were premature beats, paroxysmal tachycardia and disturbances of the pacemaker. They were not associated with demonstrable changes in the circulation, and seemed to be without clinical significance.

THE ELECTROCARDIOGRAM AND BLOOD PRESSURE
DURING SURGICAL OPERATION AND
CONVALESCENCE

EFFECT OF ROUTINE PREOPERATIVE DIGITALIZATION *

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The influence of preoperative digitalization on the incidence of post-operative complications and deaths due to "circulatory failure" is a matter of considerable interest to most surgeons, but one which has apparently received little systematic investigation. A number of observers advocate the routine employment of the drug in certain types of cases or operations, and feel that it is of undoubted value. Thus, Lilienthal,¹ in discussing resection of the lung for suppurative infections, says

With or without sepsis, it is the power of the heart to adapt itself which is perhaps the greatest factor in determining resistance. While this is practically so in all surgery, it appears to be more striking in resection of the infected lung. In any event, digitalization should be accomplished in the forty-eight hours preceding operation.

Similarly, Thomas,² in his discussion of the factors responsible for mortality after prostatectomy, says

For years I have digitalized these (prostatectomy) patients as a routine before and after operation, and thereby avoid in many cases drops in pulse pressure that not infrequently prove fatal in undigitalized patients who have been operated on. Not only will this practise save many lives, but it will surely prevent many postoperative complications and promote convalescence.

The presence of arteriosclerosis is regarded as an indication for preoperative digitalization by Richardson,³ who writes "In spite of the modern skepticism about the use of digitalis in patients with arteriosclerosis, I feel sure that it is of considerable value in tiding over the period of depression that often follows operations on old people." That the drug may be effective in lessening postoperative pneumonia is the

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1 Lilienthal, H Resection of the Lung for Suppurative Infections, Ann Surg 75 257 (March) 1922

2 Thomas, B A Factors Responsible for Reduction of Mortality and Morbidity in Prostatectomy, J A M A 82 281 (Jan 26) 1924

3 Richardson, F L Heart Lesions in Anesthesia Am J Surg (Anesthesia Supplement) 33 109 (Oct) 1919

belief of Elwyn,⁴ who thinks "it is probable that hypostatic congestion of the lungs may at times be prevented by the preoperative use of digitalis, especially in cases with a tendency towards myocardial failure."

Statistical evidence in favor of preoperative digitalization has been presented by several authors. Mandl⁵ feels that he secured a reduction of postoperative pulmonary complications from 27 to 8 per cent by the use of digitoxin before operation. Geist and Somberg⁶ have noted postoperative complications in only 29 per cent of their sixty-nine digitalized patients, as against 26 per cent in thirty-nine similar patients who had not received digitalis. Geist and Goldberger,⁷ in a later article, were able to report a further reduction of such complications to 2 per cent, which they attributed to preoperative digitalization, as it is much lower than the average in undigitalized patients.

Examples of similar views as to the efficacy of digitalis in surgical patients could be multiplied without difficulty. Most authors who recommend the frequent or routine practice of preoperative digitalization attribute its beneficial effects to its action on the blood pressure, more specifically, to its action in maintaining the pulse pressure. But with the exception of the papers of Geist and his collaborators, we have been unable to find any studies of the postoperative blood pressure in digitalized patients.

In an attempt to arrive at more exact knowledge of the influence of the drug on patients subjected to anesthesia and operation, we have studied a group of thirty persons who had received full therapeutic doses of digitalis before operation. The method of study has been given in detail in the preceding paper. Briefly, it consisted of determining the blood pressure and taking electrocardiograms at frequent intervals throughout operation, and observing any factors in the administration of the anesthetic or the surgical procedure which might be responsible for changes. After operation, the blood pressure was determined at regular intervals every day for at least ten days, and careful notes made as to the progress of convalescence and the occurrence of complications. The only selection of patients was such as to ensure a wide variety of ages and surgical conditions, as in the previous study, an attempt was made to secure only the more serious operations.

Within the two or three days preceding operation, each patient received by mouth the full amount of the calculated therapeutic dose of

4 Elwyn, H. Postoperative Pneumonia, *Anesthesia & Analgesia* **3** 43, 1924.

5 Mandl, F. *Wien klin Wchnschr* **34** 214 (April 28) 1921, abstr., J. A. M. A. **77** 79 (July 2) 1921.

6 Geist, S. H., and Somberg, J. S. Preoperative Digitalization. A Method to Reduce Postoperative Complications, *Am J Obst & Gynec* **4** 135 (Aug.) 1922.

7 Geist, S. H., and Goldberger, M. A. Effect of Preoperative Digitalization in Reducing Postoperative Complications, *Ann Surg* **78** 693 (Dec.) 1923.

digitalis. Dosage was calculated on the basis of body weight, 1.5 gm per hundred pounds being given. The only form of the drug employed was a carefully standardized powdered leaf which has been in constant use in the medical wards of this hospital. In several instances, operation was postponed after complete digitalization had been effected, in these patients, the digitalis effect was maintained by a daily dose of 0.2 gm until the morning of operation. None was given afterward except to patients with auricular fibrillation. No other change was made in the usual preoperative preparation, which was the same as for nondigitalized patients.

Evidence of the action of digitalis was secured from the electrocardiograms, which showed the characteristic inversion of the T wave or the S-T interval in twenty-nine of the thirty cases. The one patient whose electrocardiogram did not show the usual effect has been included because he received the proper amount of the drug at an adequate interval before operation, and there was no apparent reason for its improper absorption; it is possible that the T wave in this individual was previously inverted, and had been made upright by digitalis. The change in his tracings during operation, however, has been disregarded in view of the doubt concerning digitalization.

The observations here reported are primarily for comparison with those given in the preceding paper, they have therefore been classified in the same manner. It should be noted that the same rules have been followed throughout all blood pressures have been classified with reference to their relation to the preoperative level, and differences of 4 mm or less have been disregarded. The transient rise in pressure which occurred, in most patients, during the induction of general anesthesia has also been disregarded for purposes of classification.

BLOOD PRESSURE DURING OPERATION

The record of one patient has been omitted, as the blood pressure cuff became loose during operation and subsequent observations were unsatisfactory. Of the twenty-nine patients whose records were complete, the blood pressure during operation was consistently above the preoperative level in thirteen, constantly below in four, fluctuating above and below the preoperative pressure in seven, and at the preoperative level in five. The relation of these changes to the type of anesthesia is shown in Table 1.

TABLE 1.—*Blood Pressures During Operation in Twenty-Nine Cases**

Anesthesia	Above	Below	Same	Fluctuating
Gas oxygen (nitrous oxide)	11	2	4	5
Procain	1	1		
Fther	1	1	1	2

* As compared with the preoperative blood pressure.

Five patients were in surgical shock at the conclusion of the operation, in one of them, it followed sudden profuse hemorrhage. It should be pointed out that in four patients the shock was of late development, occurring in several of them at the time of closure, and that all of these had blood pressures above the preoperative level until the rather sudden fall which preceded shock. These four cases have been included in the group with those whose pressures were constantly above the preoperative level. The fifth patient who developed shock had a steady fall in pressure from almost the beginning of the operation.

BLOOD PRESSURE DURING THE THIRTY HOURS AFTER OPERATION

The records of six patients (Cases 3, 8, 11, 19, 22 and 28) have been omitted from the following analysis, one because of sudden death five hours after operation, the other five because they were in shock at the conclusion of the operation, and their blood pressures were below the preoperative level at practically all observations during the thirty hours following. (Records of patients in shock were also omitted from the corresponding table in the preceding study.) The relation of the systolic and the pulse pressures after operation to the corresponding preoperative pressures is shown in Table 2, it is of interest to observe that the administration of digitalis did not prevent a postoperative fall in systolic pressure in a considerable percentage of the patients. The figures with regard to changes in pulse pressure are even more striking, approximately 40 per cent of the group showed a fall in pulse pressure after operation. These findings are in sharp contrast to those of Geist and Goldberger,⁷ who report that in their digitalized patients "the average drop was found to be only 3 mm within the first twelve hours, after which the tension gradually returned to normal."

TABLE 2—*Blood Pressures During the Thirty Hours After Operation**

	Systolic Pressure			Pulse Pressure		
	Above	Below	Same	Above	Below	Same
6 hours after operation	6	9	9	6	9	9
18 hours after operation	11	7	6	7	11	6
24 hours after operation	10	7	7	8	9	7
30 hours after operation	7	9	8	7	11	6

* As compared with the preoperative systolic and pulse pressures.

It is difficult to show a relation between the observed changes in pressure and the clinical course of the patient. Both systolic and pulse pressures varied considerably in individual cases, not infrequently, a patient whose pressure was below the preoperative level at the end of six hours showed a rise to or above that level at the end of eighteen hours, and vice versa. However, the clinical records show that the six patients

whose systolic or pulse pressures were above the preoperative level at the end of six hours had rapid and uneventful recoveries, of the nine patients who showed a fall in pressure at that time, one had protracted nausea and vomiting, one died on the sixth day of pneumonia, and seven had normal convalescences. With regard to the patient who died of pneumonia it should be pointed out that at three of the four observations during the first thirty hours after operation the blood pressure was at or above the preoperative level.

GENERAL POSTOPERATIVE BLOOD PRESSURES

Three patients died within two days after operation, so only twenty-seven records are available for analysis. From the second postoperative day until the end of the period of observation, the blood pressure was above the preoperative level in four patients, below in twenty, the same in two, and fluctuating within wide limits in one. The interesting feature of this observation, as of the preceding ones, is the large number of patients whose pressure fell and remained below its normal level.

COMPLICATIONS

As surgical shock occurred during, rather than after, operation in all cases, it has not been included in the postoperative complications, even though it was apparently the direct cause death in one case (Case 19). One patient died suddenly five hours after being removed from the operating room, she had appeared to be in excellent condition fifteen minutes earlier. The suddenness of death suggests a vascular accident, but necropsy was not permitted. Two patients (Cases 20 and 22) developed postoperative pneumonia on the sixth and the second day, respectively, it proved fatal in both instances. In both, it followed long operations, one performed under ether anesthesia, the other under gas-oxygen. Study of the postoperative blood pressure in these cases discloses no distinctive changes.

A summary of the observation on thirty patients, with changes in blood pressure during and after operation, is given in Table 3.

CHANGES IN ELECTROCARDIOGRAMS

Eleven patients (37 per cent) showed, during operation, changes in the electrocardiogram which had not been present in the preliminary tracings. Sino-auricular tachycardia, even though it attained a high grade, has not been included as an abnormality. The observed changes are briefly discussed below.

Premature Beats.—Ectopic beats of ventricular origin were noted only once, they occurred in an elderly patient who presented signs of arteriosclerotic heart disease and auricular fibrillation.

TABLE 3—*Blood Pressures in Digitalized Cases*

Case	Age	Operation	Length of Operation	Preoperative Blood Pressure				Postoperative Blood Pressure						General Post-operative Blood Pressure	Remarks		
				Hr	Min	Anesthesia	Sys-Dia-tole	6 Hr	18 Hr	24 Hr	30 Hr	Sys-Dia-tole	Dias-tolte	Sys-Dia-tole	Dias-tolte		
1	29	Nephrectomy	3 5	Gas oxygen	96	60	Above	100	62	110	70	108	70	112	70	Above	Obesity, hypertension
2	54	Nephrectomy	1 20	Gas oxygen	210	100	Below	184	112	228	116	222	115	100	120	Below	Died 5 hours after operation
3	68	Exploration	1 18	Gas oxygen	129	78	Below	130	75	150	80	144	72	148	84	Below	Arteriosclerotic heart disease with mitricular fibrillation
4	71	Cystotomy	1 5	Gas oxygen	150	70	Above	130	75	150	80	144	72	148	84	Below	
5	61	Cystotomy	2 25	Gas oxygen	150	110	Above	138	92	138	90	134	86	130	86	Below	
6	54	Hysterectomy	2 15	Gas oxygen	134	74	Same	130	74	122	74	130	72	128	78	Below	
7	37	Hysterectomy	1 35	Gas oxygen	118	68	Fluctuating	110	74	120	73	122	78	120	80	Below	
8	35	Hysterectomy	2 25	Gas oxygen	112	70	Above	88	70	106	88	104	76	88	70	Below	Shock
9	27	Hysterectomy	1 30	Gas oxygen	106	70	Above	108	70	114	82	104	80	114	78	Above	
10	24	Hysterectomy	1 40	Gas oxygen	130	70	Same	108	18	136	80	134	78	132	74	Below	
11	63	Cholecystectomy	2 45	Gas oxygen	118	86	Above	114	90	114	90	112	86	112	80	Below	Shock following hemithigle
12	18	Cholecystectomy	1 30	Gas oxygen	116	70	Above	110	78	140	72	128	70	120	68	Same	
13	39	Cholecystectomy	1 39	Gas oxygen	130	80	Fluctuating	122	82	118	81	118	82	124	92	Below	
14	47	Cholecystectomy	2 30	Gas oxygen	120	76	Fluctuating	130	80	141	92	114	88	142	92	Deeply jaundiced	
15	51	Cholecystectomy	1 10	Ether	164	98	Below	162	108	164	112	172	122	162	110	Above	
16	15	Appendectomy	1 5	Ether	130	76	Above	130	78	138	80	130	76	138	76	Below	
17	25	Appendectomy	1 25	Gas oxygen	122	80	Fluctuating	122	68	132	66	132	72	124	71	Below	
18	41	Herniotomy	4	Local	138	98	Fluctuating	144	100	138	96	138	94	134	98	Below	
19	64	Resection of stomach	2 45	Local	112	80	Steady fall	112	90	146	90	134	84	142	92	Below	
20	19	Resection of stomach	4 10	Gas oxygen	146	90	Fluctuating	134	68	149	80	150	80	134	72	Above	
21	10	Resection of stomach	3 5	Gas oxygen	120	70	Above	126	68	149	80	150	80	134	72	Above	
22	38	Brown tumor of breast	3 25	Gas oxygen	160	100	Same	134	82	119	76	170	100	148	82	Below	
23	68	Amputation of uterus	2 55	Gas oxygen	168	98	Fluctuating	120	62	128	62	138	70	140	72	Below	
24	28	Ventral suspension of uterus	1 25	Gas oxygen	96	54	Same	126	94	116	82	114	78	110	76	Fluctuating	
25	18	Perineal repair	1 25	Gas oxygen	142	94	Above	120	64	132	70	130	62	114	66	Below	
26	15	Osteotomy	2 30	Gas oxygen	130	68	Same	132	82	134	88	136	80	124	78	Below	
27	10	Reduction testis	1 25	Gas oxygen	130	68	Same	126	64	114	70	112	68	112	68	Same	
28	24	Partial thyrodecom-	2 25	Gas oxygen	150	85	Above	148	82	148	82	153	74	148	74	Shock	
29	63	Ligation, superior thyroid artery	55	Local	210	78	Fluctuating	200	78	202	76	196	70	175	68	Below	
30	22	Cardiopathy	1 10	Local	115	70	Above	124	80	128	86	126	82	126	80	Below	

Reversal of T Wave—In four patients, there occurred a partial or complete reversal of the T Wave in Lead II, which had become inverted through the action of digitalis. The change was transient, but, in every instance, it recurred at intervals throughout operation. Without exception, it appeared in association with a notable increase in heart rate, when the rate fell to its usual level, the T wave became again inverted. All patients who showed this reversal were anesthetized with nitrous oxide and oxygen. Age had no apparent influence on its incidence as the ages of the patients varied from 15 to 48 years. That the change may have been due to vagal release is suggested by its invariable association with an increased rate of beating. The character of the reversal is shown in Figure 1, A and B.

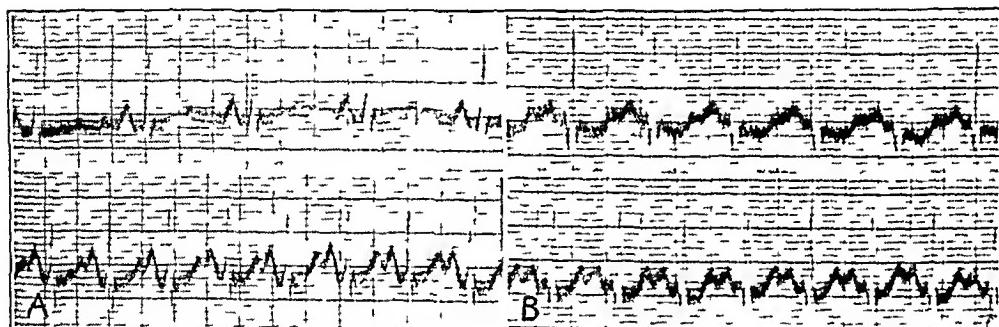


Fig 1.—Lead II change in T wave and S-T interval in lower tracings. Increase in rate in A is from 90 to 166 a minute, in B, from 124 to 162. In this and the following electrocardiograms, distances between abscissas represent 10^{-4} volts, and time is in one-fifth seconds.

Paroxysmal Tachycardia—Paroxysms of auricular tachycardia were registered in three patients, one of them also had paroxysms of ventricular origin. From the standpoint of the anesthetic employed, these cases afford an interesting contrast to those mentioned in the preceding paper. The two patients in that series who developed paroxysmal tachycardia both received ether through a nasal tube introduced into the pharynx, of the three patients in the present series, one was anesthetized with nitrous oxide and oxygen, and two with procain. With regard to possible factors concerned in the etiology of the paroxysms, it should be noted that two patients had unequivocal signs of heart disease, one of arteriosclerotic and the other of rheumatic origin, while the third had shown for a long period the continuous tachycardia associated with exophthalmic goiter. Two of the patients developed profound shock during operation, but no paroxysms were noted clinically or in the electrocardiograms after the blood pressure had fallen below 80 mm of mercury. The tracings of two patients are reproduced in Figures 2 and 3.

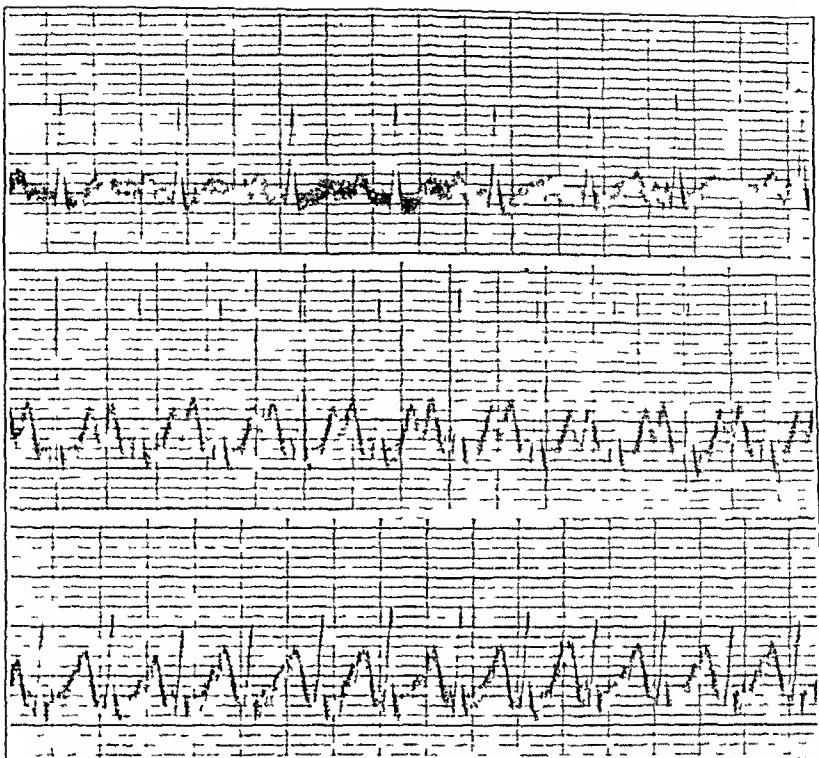


Fig 2—Lead II upper tracing shows normal mechanism, with some depression of the S-T interval, middle record shows sino-auricular tachycardia, with a rate of 184 a minute, lower tracing was taken during a paroxysm of tachycardia, the rate being 202

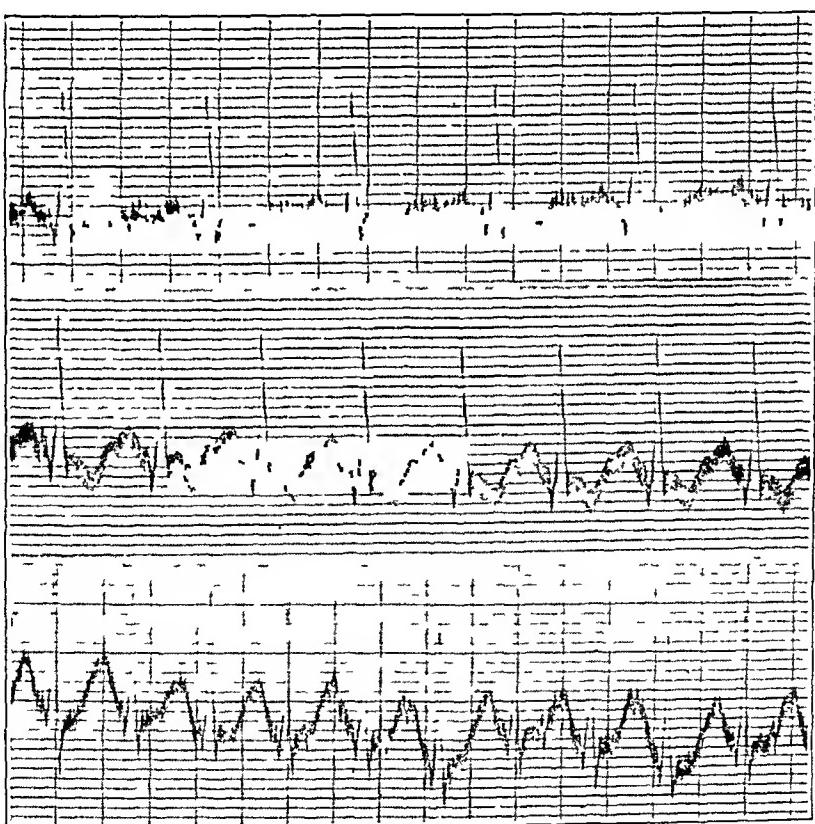


Fig 3—Lead II upper shows normal mechanism, with depression of the S-T interval, middle shows a deep inversion of the T wave during operation, lower is thought to represent a paroxysm of tachycardia, although it is possibly sino-auricular tachycardia, with reversal of the previously inverted T waves, the rate being 180 a minute

Displacement of the Pacemaker —A disturbance of the pacemaker, as evidenced by a disappearance of the P wave in the electrocardiogram, was noted in three cases. In none of them were there coincident alterations in any other deflections. In no instance was there any apparent change in the circulation or blood pressure which could be attributed to the altered cardiac mechanism. It is true that, in all three cases, the blood pressure was above the preoperative level at the time the abnormal tracings were secured, but the elevation in pressure had occurred before the abnormality appeared in the electrocardiograms, and persisted after normal mechanism had been restored. All three patients were males, all received nitrous oxide and oxygen as the anesthetic. As in previous examples, the change in the electrocardiogram appeared only during the earlier part of the operation.

TABLE 4.—*Electrocardiograms and Blood Pressures*

Case	Age	Cardiac Diagnosis	Preoperative Blood Pressure		Abnormalities in Electrocardiograms	Simultaneous Blood Pressure		Remarks
			Sys. tolic	Dias. tolic		Sys. tolic	Dias. tolic	
4	71	Arteriosclerotic heart disease auricular fibrillation	150	70	Fetopis ventricular beats	180	96	
5	61	Normal	150	110	Displacement of pace maker	188	104	
10	24	Normal	130	70	Reversal of T wave	128	72	
12	48	Normal	116	70	Reversal of T wave	140	70	
14	47	Normal	120	76	Displacement of pace maker	148	90	
19	64	Arteriosclerotic heart disease	112	80	Paroxysmal tachycardia (auricular and ventricular)	96	76	Carcinoma of stomach
20	49	Normal	146	90	Displacement of pace maker	156	92	
21	40	Normal	120	70	Reversal of T wave	138	78	
26	15	Normal	130	68	Reversal of T wave	128	80	
28	24	Thyroid heart disease (?)	150	85	Paroxysmal tachycardia (auricular)	122	96	Thyrotropinosis
30	23	Rheumatic heart disease	110	60	Paroxysmal tachycardia (auricular)	154	*	Adherent pericardium
						124	*	

* Diastolic pressure questionable as sounds were audible without inflation of cuff.

RELATION OF ELECTROCARDIOGRAPHIC CHANGES TO BLOOD PRESSURE

So far as could be observed, there was no relation whatever between the blood pressure and changes in cardiac mechanism. This complete absence of correlation was found to apply not only to such minor and transient changes as alterations in the T wave and occasional premature beats, but also to such profound disturbances as prolonged paroxysms of tachycardia. In only one instance was there an apparent relation between an abnormal mechanism and a change in blood pressure—the onset of a paroxysm of tachycardia (as determined by auscultation and

graphic records) seemed to be accompanied by a sharp rise in pressure, but similar rises occurred several times after the end of the paroxysm, and a subsequent episode was not associated with an alteration in the blood pressure.

A summary of the electrocardiographic changes and the associated alterations in blood pressure is given in Table 4. Where two blood pressures are recorded, they represent the readings taken simultaneously with the first and last electrocardiograms that showed the abnormality.

RELATION OF ELECTROCARDIOGRAPHIC CHANGES TO CARDIAC PATHOLOGY

Only four of the thirty patients studied had clear signs of heart disease (Cases 4, 20, 29 and 30), while a fifth (Case 28) was thought to have early changes in the heart of the type associated with some instances of exophthalmic goiter. Of these five, four showed changes in the electrocardiogram during operation. Paroxysmal tachycardia unquestionably stands first in importance among the changes found in this study, and it is worthy of note that of the three patients whose records displayed this abnormality, two had definite heart disease and the third very probably had myocardial damage. There were symptoms and signs of slight congestive heart failure in two cases (Cases 20 and 29), none gave a history of anginal pain.

It is thus seen that four of the five cardiac patients (80 per cent) developed some abnormality of the heart's mechanism during operation, while only seven of the twenty-five normal patients (28 per cent) showed any changes, and these were extremely slight.

SIGNIFICANCE OF ELECTROCARDIOGRAPHIC CHANGES

Five patients developed the picture of surgical shock during operation, two of them had shown paroxysms of tachycardia earlier. The relation of the arrhythmia to the subsequent development of shock seems problematical, for one of these patients had degenerative changes in the heart and a systolic blood pressure below 100 mm of mercury at the time operation was commenced, while the other had a severe form of exophthalmic goiter, a serious operative and postoperative course was therefore to be expected in both. Furthermore, in one patient, the paroxysms were first detected after the fall in blood pressure was noted, and, in the other, the paroxysms had ended about twenty minutes before the pressure began to decline. It is unlikely that paroxysms occurred which escaped detection, for the condition of the latter patient was so critical that the heart rate was counted through the blood pressure attachment at intervals of about one minute, and electrocardiograms were taken at every indication of a change.

There was no evidence obtained to indicate that the other abnormalities in the electrocardiograms were of the slightest clinical significance

COMPARISON OF DIGITALIZED AND UNDIGITALIZED PATIENTS

With respect to the period of anesthesia and operation, blood pressures which fluctuated above and below the preoperative level were noted in a considerable number of the patients who received digitalis, as compared with those who did not. The general level of the blood pressure during operation was above the preoperative pressure in a larger proportion of the digitalized than of the nondigitalized patients. There appears to be a measurable difference between the two groups in these respects, but, in estimating the value of digitalis, it should be remembered that such differences in pressure have seemed to be without clinical significance.

It is with regard to the changes in blood pressure during the first thirty hours after operation that the most interesting observations have been made. There is apparently a widespread assumption that many postoperative complications and deaths are due to a failure of the circulation which manifests itself objectively through a fall in the systolic pressure or pulse pressure or both. We have already mentioned our failure to find any such postoperative fall in the majority of nondigitalized patients, even in those who developed pulmonary or other complications during convalescence. Of the digitalized patients, however, a high percentage showed a significant lowering of both systolic and pulse pressures during the thirty hours after operation. The actual percentage of the patients in each group who showed this postoperative fall in systolic and pulse pressures is shown in Table 5.

TABLE 5.—Percentage of Patients Showing Postoperative Fall in Systolic and Pulse Pressures

	Systolic Pressure		Pulse Pressure	
	Nondigitalized, per Cent	Digitalized, per Cent	Nondigitalized, per Cent	Digitalized, per Cent
6 hours after operation	30	37.5	34.6	37.5
18 hours after operation	19	29	30	46
24 hours after operation	24	29	32	37.5
30 hours after operation	11.5	37.5	16.6	46

The changes in blood pressure from the second postoperative day onward have attracted little attention from previous observers, but in this period also there is found the same relative difference in the two groups. Nearly three-fourths (73 per cent) of the digitalized patients had blood pressures during convalescence well below the preoperative level, while only 43 per cent of the nondigitalized patients showed a similar lowering.

Concerning changes in the electrocardiogram during operation, the figures appear to indicate that abnormalities occurred less frequently in

the digitalized patients, also that displacements of the pacemaker were less frequent, and paroxysmal tachycardia more frequent, in this group. The differences in the two groups, however, are slight, and no significance can be attached to them when the method of study is considered. Electrocardiograms were taken from most patients only once every five minutes, and the abnormalities rarely appeared in more than two of the twenty or thirty records secured. The actual incidence of changes could be determined only by means of continuous tracings, an apparent slight reduction in the number of abnormalities, therefore, cannot safely be accepted as indicating an actual reduction. That the observed changes were without apparent clinical significance has already been mentioned.

With regard to complications and deaths in the two groups, it is difficult to make a satisfactory comparison. Meager figures indicating the number of postoperative complications and deaths are available, but cannot justify any conclusions. For instance, pneumonia occurred in four nondigitalized patients and in two who had received digitalis. It seems unfair, however, to maintain that the incidence of that disease is twice as great in the first group as in the second, because two of the four patients in the first group who developed pneumonia had prolonged and extensive operations on the jaw, tongue, pharynx and neck, with unquestionable inhalation of septic material. It is hardly conceivable that the preoperative administration of digitalis would have prevented the development of pneumonia in either of these patients. Similarly, we find recorded four deaths among the digitalized patients, as against two in the nondigitalized group, but analysis of the histories reveals that of the four digitalized patients who died, one had advanced heart disease and one a practically inoperable brain tumor. A third patient died suddenly and the cause was undetermined. The behavior of the blood pressure has been of no value in either group. Surgical shock, which has seemed to us an operative, rather than a postoperative, complication, occurred an equal number of times in both groups.

A careful consideration of all the known factors in those patients who developed postoperative complications seems to warrant the conclusion that their incidence in both the digitalized and undigitalized patients was about what would have been anticipated, and that it affords no evidence of a beneficial influence on the part of digitalis.

COMMENT

It is obviously impossible to draw any final conclusions from a study which has included a comparatively small number of patients and a wide variety of ages and operations. The observations here reported may not be strictly comparable with those of previous authors but they

are fairly comparable with those given in the preceding paper. The patients who composed the two contrasting groups were drawn from the same wards, were under the same preoperative and postoperative regimen, were anesthetized and operated on by the same group of anesthetists and surgeons. All observations were made by the authors. It is therefore of some interest to find that the preoperative administration of digitalis has not only failed to prevent a postoperative fall in systolic blood pressure and pulse pressure, but has possibly caused such a fall in a large number of patients. It has had no apparent influence on the incidence or severity of postoperative complications. To conclude that digitalis is without value in preventing such complications would be to go beyond the observed facts, it can probably be said with fairness, however, that this study has afforded no support for the belief that there are important changes in the blood pressure after operation which can be prevented by the earlier administration of digitalis. Whether observations on a large group of elderly patients subjected to the same anesthetic and operation would yield similar results is open to question.

SUMMARY

The blood pressure was determined, and electrocardiograms taken, at frequent intervals during anesthesia and operation in thirty patients who had been completely digitalized. Blood pressures were determined and notes of the clinical condition made at regular intervals every day for from eight to eighteen days after operation.

The blood pressure, during operation, varied considerably in individual cases. A large proportion (45 per cent) maintained the pressure above the preoperative level, and about one-fourth showed wide fluctuations above and below the preoperative pressure.

A considerable number of the patients showed a fall in the systolic blood pressure during the thirty hours following operation. An even larger number showed a decrease in the pulse pressure. These changes seemed to have no relation to the clinical course or the development of complications.

The blood pressure after the second postoperative day was below the preoperative level in more than two thirds of the patients. Its behavior, during this period, was found to be of no value in estimating the rapidity of convalescence.

Electrocardiograms taken during the operation showed changes not present in preliminary records in about 37 per cent of the patients. The most frequent of these changes were displacement of the pacemaker, reversal of an inverted T wave in Lead II and paroxysmal tachycardia. They were unaccompanied by clinical evidences of circulatory disturbance.

A comparison of the observations on digitalized and nondigitalized patients discloses only few differences. There was a postoperative fall in systolic and pulse pressure in a greater proportion of the digitalized patients than of the nondigitalized. No evidence was secured of a beneficial effect of digitalis on postoperative complications or deaths.

CONCLUSION

There is no convincing evidence that the preoperative administration of digitalis exerts a favorable influence on the blood pressure or the incidence of postoperative complications in a group of unselected patients. There is suggestive evidence that the drug tends to cause the precise change in blood pressure which it is usually given to prevent. There is no apparent necessity or justification for its routine employment in patients who possess normal hearts.

THE INVOLUNTARY NERVOUS SYSTEM AN IMPORTANT FACTOR IN THE BODY'S RESISTANCE¹

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I

Infection and body resistance have been studied from various angles for several centuries

Empirically, nonspecific therapy has been practiced in different forms for an equal period of time, and only of late has scientific endeavor been applied to solve the problems to which the uses of such agents have given rise

Petersen¹ has particularly emphasized the rôle that body resistance plays in the administration and the results of nonspecific treatment

Our aim has been to determine the physiologic basis of this resistance, in other words, to point to certain organs whose common functions were practically synonymous with resistance. We believe that resistance is a product of the functions of various organs and it is quite probable that these organs possess additional functions that are exercised normally in the course of biologic processes. The functions of resistance are normally inherent in the body but, under healthy conditions, their activity is restricted to a minimum, in other words, they may be regarded as latent. When infectious conditions prevail, evidences of their existence become apparent (as in the production of leukocytes and antibodies), but there is nothing to indicate that such an increased function is to be regarded as in any way abnormal or as an abnormal function of the organ involved, on the contrary, it is a natural manifestation of the body's inherent resistance powers.

Our studies were undertaken with the intention of determining (1) the organs of resistance, and (2) how the stimulation to increased activity reaches these organs, and the manner in which this impulse is conducted to the site of infection.

Our experiments to date lead us to the opinion that the entrance of bacterial excitants into the body causes a reaction involving, besides others,² chiefly two groups of organs (1) the bone marrow system,³

¹ From the department of dermatology and syphilology, College of Physicians and Surgeons, Columbia University

¹ Petersen, W F Protein Therapy and Nonspecific Resistance, New York, Macmillan Company, 1922

² Jobling, I W, and Petersen, W F J Exper Med **22** 141, 1915, Bacteriotherapy in Typhoid Fever, J A M A **65** 515 (Aug 7) 1915, Nonspecific Factors, J A M A **66** 1753 (June 3) 1916 Jobling, J W Nonspecific Substances, Arch Int Med **19** 1042 (June) 1917 Larson, W P Minnesota Med **2** 332 (Sept) 1919

³ Gay, F P, and Claypole, E J Arch Int Med **14** 662 (Nov) 1922 Muller, E F Med Klin **14** 440, 1918, Beitr z Klin d Infektionskr **8** 34, 1919

the originator of the white blood corpuscles and probably also the source of the carriers of specific resistance (such as agglutinins), (2) the involuntary nervous system,⁴ the conductor not only of the stimulation from the site of infection to the bone marrow system but also of the newly formed immunizing substances and leukocytes to the site of infection.

In what follows, reference will be made only to the importance of the involuntary nervous system as a major factor in nonspecific and specific resistance.

In this connection, we accept as a postulate that the vascular system is the principal field of manifested and measurable activity of the involuntary nervous system.

The vasodilatation by the parasympathetic portion of the involuntary nervous system and the vasoconstriction by its sympathetic portion are, under normal conditions, in that state of regulatory equilibrium that is demanded by the nutritive and functional synergism of the organs. We know of influences of various kinds, acting in the main on the body from without, which disturb this equilibrium by giving a preponderating influence to one or to the other of these two antagonists. Less known to us, however, are the paths of stimulation on which these impulses of the involuntary system operate and thus lead to changes in the equilibrium of the blood vessel tonus.

Muller and Glaser-Hahnstein⁵ point to the everyday occurrence of a unilateral blood vessel innervation by psychic processes and have experimentally shown that the midbrain, the thalamus opticus and the central gray matter of the third ventricle are to be regarded as the places where strong sensory stimuli, as well as those changes in the general irritability caused by changes of mood, pass over to vasomotor channels. They thus discovered one anatomically important part of this path of stimulation, over which pass the vasomotor impulses, whose causes and purpose are still unknown to us.

We may further mention that, pharmacologically, the vasodilatation produced by pilocarpin and the vasoconstriction produced by epinephrin, both of which influences originate in the artificially caused preponderance of one of the factors of the vascular tonus under normal conditions, are at equipoise. For this reason, these alkaloids produce a genuine disturbance in the regulation of the circulatory system. The well known final effect of these disturbances makes it possible for us to ascertain which of the two factors has gained the preponderance in an individual case, and thus points out the right road in the search for the cause.

⁴ Muller, E F Munchen med Wchnschr **70** 1163 (Sept 14) 1923, Arch f Dermat u Syph **145** 188, 1923

⁵ Muller, L R Autonomes Nervensystem, Berlin, 1923

Another well known change in the vascular tonus, a vaso dilatation, for the most part strictly localized, is caused by almost all inflammatory irritations. It is true, however, that the question has not as yet been definitely decided whether we have here to deal with genuine disturbances of vasomotor regulation produced by external causes, or whether we must regard this dilation of the blood vessels as a reflex alteration of the local condition of the tissues. The latter explanation is more acceptable, according to the modern view of the problem of inflammation, but the hypothesis of a specific excitation of the vasodilators, put forward by Meyer and Gottheib,⁶ has not been verified as yet with respect to causation or to purpose. On the other hand, it has been experimentally proved, according to the same authors, that a stimulus to the vasodilators is followed, first of all, by an acute hyperemia, and subsequently by an increase in the permeability of the vessels.

II

Processes in the circulation originating, in the last analysis, from completely different causes, and which may be recognized by signs that have seemingly nothing to do with those previously described, have led us to a new and clearer insight into the regulation of vascular tonus, and have made it possible to explain many well known phenomena.

Goldscheider and Jacob⁷ described, as early as 1894, an acute leukopenia resulting from the intravenous injection of peptoid bodies. These results led to the concept of the "peptone shock" manifesting itself in the blood by a displacement, of short duration, of the leukocytes, principally the neutrophil polymorphonuclears, of which, in this test, a great number disappear for a short time from the peripheral blood and must therefore be retained in the vessels of the inner organs.

In 1920, Widal⁸ published an observation, similar in effect. He noted in patients with liver diseases, after alimentary irritation (200 gm of milk taken on an empty stomach), a leukocyte fall of short duration accompanied by a slight fall in the blood pressure and alterations in the viscosity and index of refraction of the blood, he designated this phenomenon as "crise haemoclasique." He explains it as follows: Those constituents of food which have neither been assimilated nor completely split up pass normally through the intestinal walls into the blood of the portal vein, they are then retained by the liver, detoxicated,

6 Meyer and Gottheib *Pharmakologie*, Berlin, 1923

7 Goldscheider and Jacob *Ztschr f klin Med* **25** 373, 582, 1894

8 Widal, F., Abramé, P., and Brissaud, D. *Presse med* **28** 181 (April 3) 1920

and thus removed from the general circulation. He concluded this was a normally present poison-removing function of the liver and termed it "proteopoxic." A disturbance of this function would then cause an acute leukopenia, as a result of the entrance of peptonoid bodies in the general circulation.

This explanation was inconceivable to us because clinical and experimental observations, which will be mentioned later, led to the belief that the leukocyte fall was caused by disturbance of the involuntary nervous system, and we further assumed that this phenomenon is only represented by an acute displacement of the leukocytes.

III

These conclusions were reached after the following experiments, beginning again from an entirely different angle. In the course of extensive investigations on the rôle of the skin in immunizing processes, which were reported in a series of papers, we observed a new cause for the acute temporary leukocyte impoverishment of the peripheral vessels.⁹

We found that injections of physiologic sodium chloride solution and other nonirritant substances given intracutaneously led to a dilatation and to an increase in the number of leukocytes in the vessels of the subcutis. On the other hand, after subcutaneous injections, despite the proximity of the vessels, a dilatation never takes place.

These simple experiments prove that it is not the injected material but the place and the manner in which the injection is made into the derma that cause these dilatations of the vessels and the accumulation of leukocytes in the latter.

Thus is proved an influence, originated in the skin, which stimulates the vasodilating nerves of the subcutis. We do not know if such an experiment is equal to an infection produced by germs entering the skin. We further do not know if the reaction of the vessels of the subcutaneous tissues by dilating is a part of a local resistance. In any event it is the beginning of an active process in connection with the injected agents. Later, it will be observed that leukocytes, accumulating in the dilated vessels of the subcutis, penetrate the walls, enter into the tissues and reach the skin, more particularly the area around the injection.¹⁰

We further determined, by other experiments, that intradermal injections of minute quantities of physiologic sodium chloride solution, distilled water, lactalbumin, milk or even air, cause an immediate and

⁹ Muller, E F Arch f Dermat u Syph **31** 237, 1921, Munchen med Wchnschr **68** 912 (July 22) 1921, ibid **69** 1506, 1753, 1922, ibid **71** 202 (Feb 15), 672 (May 23), 813 (June 20) 1924, ibid **72** 125, 1925

¹⁰ Muller, E F Arch f Dermat u Syph **31** 237, 1921

sudden fall of the leukocytes in all of the vessels of the periphery.¹¹ These leukocytes will suddenly be found in the strongly dilated vessels controlled by the splanchnic nerve, especially in the liver. These findings have been proved, in recent experiments, by injecting rats with arsphenamin.¹² These observations coincide with the findings of Dean,¹³ who discovered a very large number of leukocytes in the dilated liver vessels, more particularly in the smaller, in a patient who suddenly died of an anaphylactic shock. The dilatation of the subcutaneous vessels, situated immediately under the area of injection, as well as the enormous distention of the abdominal vessels, were due to the occurrence of an acute preponderance of the vagotonus, caused by a reflex to the parasympathetic part of the involuntary nervous system.

We succeeded in eliminating this reflex by blocking the parasympathetic nervous system (1) in the skin, and (2) in the abdominal region. It is further possible to bring about the reflex with direct pharmacologic stimulation of the parasympathetic nervous system by pilocarpin or to postpone it by adding epinephrin to the injected fluid. Thus, it was proved that stimulation of the skin changes the balance of the involuntary nervous system not only at the site of injection, but also in the region of the organs controlled by the splanchnic nerve.¹⁴

More recent experiments demonstrated that the parasympathetic vasodilatation leads to an accumulation of leukocytes at these dilated parts of the circulatory system. Thus has been found the direct relation between the skin and the leukocytes in the blood stream. The existence of this connection and its importance for every skin stimulation is enhanced by the determination that other stimulations, such as freezing, application of heat and Ponndorf's scarification, lead to a like effect on the parasympathetic nervous system.

For example, if in chronic gonorrhea strong or weak stimulations of the skin are employed, an abundance of young and fresh leukocytes are produced and can be found in the excretion of the urethra, where they were previously found only in very small numbers.

The foregoing investigations explain this phenomenon in the following manner. As in every other acute and chronic infection, there is in urethral gonorrhea a local overbalance of the parasympathetic tonus recognizable by the inflammatory vasodilatation. This is in the main similar to local findings subsequent to intradermal injections.

11 Muller, E F Ztschr f d ges exper Med **32** 120, 1923

12 Muller, E F, and Myers, C N Proc Soc Exper Biol & Med **21** 474, 1924

13 Dean J Path & Bacteriol **25** 3, 1920

14 Muller, E F, and Holscher, R Ztschr f d ges exper Med **61** 225, 1924

While the described skin stimulation is held in balance by the sympathetic nervous system in all vascular regions, with the exception of the site of injection and of the visceral area, this equilibrium is also missing at the site of inflammation, because it is subjected to a constant overbalanced tonus of the local fibers of the parasympathetic nervous system. This overbalance of the parasympathetic tonus is further increased by the sudden stimulation emanating from the skin, and now there occurs the phenomenon that is described above as relating to the increase of leukocytes, the leukocytes in the blood stream are fixed along the walls of the blood vessels, later penetrating the walls and entering the bacterially endangered parts. We are not positive whether this penetration is due to chemotaxis or to impulses inherent in the leukocytes, whichever it may be, the fact remains that they are found in the tissues and in the excretion, where formerly they were absent.

This reaction can also be inhibited by the administration of epinephrin or atropin and not by pilocarpin, thus proving that an undisturbed parasympathetic system is necessary for this reaction.

It is of further interest that the beginning of the leukocytosis is connected with a similar parasympathetic influence on the dilatation of the blood vessels of the bone marrow system¹⁵.

No conclusive explanation for the transmission of a stimulative impulse was evident from the findings in the cellular marrow of the vertebrae. More favorable conditions obtain in the fatty bone marrow tissue of the long bones. In acute infectious conditions (for instance, pneumonia), a dilatation of the vessels with resulting hyperemia, followed by vascularization and the first appearance of myeloid elements in what was formerly only fatty tissue, is observed in this area. There is no doubt that this process, an independent reaction of the organism, is based on a change of tonus in the vascular nerves. Vasodilatation, in other words, stimulation by way of the parasympathetic system, predominates, and the assumption is therefore justified that this stimulation, similar to the remote effect on the vessels of the splanchnic area, originates in the vicinity of the site of infection.

From a purely objective point of view, this process is entirely non-specific, for it is not possible to prove that the ferment contained in the leukocytes and also in the serum can be produced by merely transmitting a kinetic impulse to the myeloid system by way of the involuntary nervous system.

There is only one exception. In acute cases of infectious diseases, as in pneumonia, the cells of the vertebral marrow do not possess any distinct bactericidal properties. The cellular tissues of the long bones,

15 Muller, E F Virchows Arch f path Anat 246 50, 1923

however, which are formed during the progress of the disease, are decidedly bactericidal, thus preventing the excitants, circulating in the blood, from taking a foothold. In this instance, the identical stimulative process furthers the formation of cells with specific properties.

IV

These tests were not sufficient proof that specific stimulation can also be transmitted along the involuntary nervous system. The following investigations, however, may be accepted as conclusive.

They were made with insulin and rabbits were used for the tests.¹⁶ The tests were carried out as follows. Rabbits were fasted for from eighteen to twenty hours, and their blood sugar was determined. They were then injected with equal quantities of insulin, simultaneously, by both the subcutaneous and the intradermal route.

Banting and Best have designated 1 unit of insulin (per kilogram of body weight) as the quantity required for subcutaneous injection to decrease the blood sugar of a normal rabbit from about 0.1 to 0.11 per cent to about 0.045 per cent. This has since been accepted as the physiologic unit for insulin treatment.

In comparing the results of the subcutaneous and the intradermal methods of administration, it will be found that the effect of an equal dose of insulin is considerably prolonged if given by the intradermal route. This is rather remarkable and difficult to explain. It should be noted that factors of resorption alone could not explain these variations, for practically the same effect on the blood sugar is evident with both methods within a period of two hours. If, after intradermal injection only part of the injected insulin can take effect immediately, due to slow resorption, surely the effect on the blood sugar cannot be equal to that produced by the larger quantity of insulin that is absorbed immediately after subcutaneous injection.

Assuming that a subcutaneous dose is resorbed within thirty minutes after administration, this would by no means afford an explanation for the increased effect observed after intradermal injection that is of equal intensity, yet is of two hours' longer duration. In animals after intradermal injection, the wheal disappears comparatively soon, it is never visible longer than thirty minutes. Even if it is assumed that the difference in reaction of the two methods of injection is due to the slower resorption by the intradermal route, it would be expected that the period of initial low sugar would merely be postponed. Furthermore, the delay might be expected to last a little longer than the time during which the wheal is discernible. This explanation becomes

16 Muller, E. F., and Corbitt, H. B. J. Lab. & Clin. Med. 9: 608 (June) 1924.

improbable when it is considered that the lowest value of the blood sugar for both methods is reached after from one to two hours, the difference existing solely in the period during which this low value is maintained.

Summarizing our experiments There is evident, after intradermal administration, a considerable prolongation of the effect of insulin on the blood sugar of normal rabbits At first we were not able to give an explanation of these facts

Beyond doubt, the skin as an individual organ is partly responsible for this effect, also, the factor of resorption plays an important part However, the foregoing alone does not suffice to explain this phenomenon

The following is of importance¹⁷ The effect of insulin injections increases proportionately to the distance from the circulatory system at which the injection is made, in other words, intravenous injections are the least effective, intramuscular and subcutaneous injections are considerably more effective and intradermal injections have the greatest effect of all

These findings suggest a comparison with the former tests with nonspecific agents Their effect also is greatly enhanced by the intradermal method of injection while equal doses administered subdermally are ineffective, and it has been definitely determined that this increased effectiveness is due to the close relation of the skin to the involuntary nervous system

We were, therefore, led to assume that there exists a similar path of conduction by way of the involuntary nervous system When we recall the highly interesting investigations of Meltzer and Kleine,¹⁸ this assumption gains in strength The authors determined that the effect of epinephrin on hyperglycemia is inversely proportional to the rate of its introduction into the circulation, in other words, the effect is only slight after intravenous injection and is considerable after subcutaneous injection Our most recent, as yet unpublished, investigations indicate that intradermal injection in these cases, in certain limits, will increase or prolong the effect

Additionally there is the significant determination that even entirely nonspecific agents, such as sodium chlorid solutions, will effectually increase the blood sugar if injected intradermally

It is quite obvious that former methods of investigation suggested themselves We therefore attempted to block the involuntary nervous

17 Corbitt, H B J Am Pharm A **14** 108 (Feb) 1925 Muller, E F, and Corbitt, H B J Lab & Clin Med, to be published

18 Meltzer and Kleine Rockefeller Inst Pub **19** 146, 1914

system. The results of such tests with epinephrin and insulin are known. Epinephrin diminishes the effect of insulin. There is no doubt that epinephrin increases the tonus of the sympathetic nervous system so that we suspect there may be a connection between these facts. This gains more importance when one remembers that atropin also diminishes the effect of insulin. Magenta and Biazotti¹⁹ arrive at similar results. This may be explained as follows. Epinephrin increases the tonus of the sympathetic nervous system and has a depressing and paralyzing effect on the parasympathetic nervous system. Atropin has, to a certain degree, a directly paralyzing effect on the parasympathetic nervous system. This paralyzing effect either diminishes or nullifies the effect of insulin. It is, therefore, feasible to conclude that the effect of insulin is conducted in part at least along the route of the parasympathetic nervous system.

Pilocarpin has no effect on insulin medication, nor has physostigmin (eserin) or nicotin, according to Magenta and Biazotti. These facts also indicate that the parasympathetic nervous system plays a part in the realization of the insulin effect, for, if the function of the parasympathetic nerves is disturbed, the effect of insulin is greatly diminished, but no stimulation of this system can affect it.

It is not our intention to draw any conclusions regarding insulin treatment and diabetes from the findings of these experiments. However, it is certain that both insulin and epinephrin affect the blood sugar content through a stimulative impulse traveling by way of the involuntary nervous system.

At the time of these studies it was not certain whether or not insulin takes effect only in the manner described, but our investigations, as well as those of other authors, have led to the conclusions that the involuntary nervous system conducts a specific stimulation without biologic contact directly to the liver or to some other organ that is responsible for the blood sugar lowering effects.

Later studies on the mechanism of insulin action carried on by the author and Dr H. J. Wiener in the Department of Metabolism, Vanderbilt Clinic, College of Physicians and Surgeons, New York, will be published shortly in this journal. They demonstrate that in human beings insulin, injected intradermally, acts in part by a nervous stimulation of the glycogenic function of the liver in the absence of demonstrable evidence of the presence of the hormone in the blood stream or in the tissues. These results show that a specific stimulus can be conveyed by the involuntary nervous system from the site of injection to a distant center.

¹⁹ Magenta, M. A., and Biazotti, A. Compt rend Soc de biol 89:1120, 1923.

v.

We have stressed the importance of the involuntary nervous system in connection with the experiments quoted, and we wish to reiterate that the involuntary nervous system is the conductor of certain impulses, that no substance, nothing material, has to pass from one organ as the first recipient of the stimulation, to the other organ, which later accepts and reacts to this stimulation.

Nothing material, merely stimulative impulses, are transmitted. This knowledge of the principles and mechanism underlying the body's resistance, in those instances, offers a new series of problems and also justifies the foregoing point of view on the problem of infection and resistance.

Summarizing, when excitants enter the body, two great systems of organs participate in setting up the ensuing reaction, either alone or in combination with others. One, the bone marrow system, the originator of the properties and the cells prerequisite for resistance, and probably also the originator of the ferments of specific resistance, the other, the involuntary nervous system, the conductor of impulses of stimulation from an infected area to the myeloid system and at the same time the regulator not only of the vessels but also of their leukocytic content.

At the site of infection, we must assume an involuntary perception of the presence of infectious material resulting in impulses that, in turn, produce a dilatation of vessels in the surrounding tissues by means of an increased tonus of the local fibers of the parasympathetic system. Simultaneously with this dilatation there is a change in the normal condition of the walls of the vessels which, as a reflex, results in an increase of leukocytes in these dilated parts.

This early local increase of leukocytes occurs without any involvement of the bone marrow system, and is the result of changes in the walls of the vessels caused by the parasympathetic system enabling the vessels to retain more leukocytes from the circulating blood.

Beside this first increase of leukocytes at the site of infection there is later observed a decided increase in the number of leukocytes in the entire blood stream due to an increased activity of the myeloid system. This produces not only the elementary cells but also their specific ferments.

The involuntary system also is vitally concerned in the production of this typical "myeloid reaction." So far, experimental investigations have not revealed the direct path along which the stimulation travels from the site of infection to the bone marrow. We know the path as far as the vessels of the surrounding tissues are concerned, and we know that from these the parasympathetic system conducts the stimulation to the abdominal vessels. But, from purely anatomic experiences

there is a high degree of probability that the stimulation is carried from the site of infection to the myeloid system by way of the involuntary nervous system. No objective findings in the bone marrow of the vertebra sufficient to serve as an explanation for the stimulative conduction have been determined. In the fatty tissues of the marrow of the long bones, conditions are more favorable. At this point, there is first observed great dilatation of the vessels filled with blood, this stage is followed by vascularization and, later, by the first appearance of myeloid elements. This dilatation is beyond doubt an independent reaction of the body produced by the nerves regulating vascular tonus. In other words, vasodilating impulses traveling by way of the parasympathetic system predominate, and we are therefore quite justified in assuming that these impulses are sent out from the site of infection, which creates a condition analogous to that of telekinetic influence on the vessels controlled by the splanchnic nerve.

The resulting increase in cell production of the myeloid system may spread to involve all portions of the bone marrow capable of transformation. If this process continues undisturbed, it will produce a total increase of normal, fully developed myeloid cells, presenting the clinical symptoms of typical leukocytosis.

As soon as this normal hyperactivity of the myeloid system increases the number of polymorphonuclear leukocytes in the circulating blood, the involuntary nervous system acts by conducting these newly formed cells to the site of infection. On reaching the dilated vessels—dilated because of the continued increase of tonus in the parasympathetic system of this area—the leukocytes are retained. Thus, the total number of leukocytes in these vessels increases at the same time that they commence to emigrate through the walls of the vessels into the tissues endangered by germs, together with the local tissue reaction, and yet distinctly individual, there are produced the clinical symptoms of an acute local inflammation. This closes the circle with the aid of the bone marrow and the involuntary nervous system, the body is thus enabled to afford a certain protection to the endangered area.

DISEASES OF THE PANCREAS
A PATHOLOGIC STUDY, WITH REPORT OF CASES
MOSES BARRON, M.D.
MINNEAPOLIS

Few diseases associated with definite organic changes present so many pitfalls in diagnosis as certain lesions involving the pancreas, which are either left undiagnosed or are diagnosed incorrectly. These are diseases associated with the function of the external secretion of the gland. There is as much confusion today on the pathology and symptomatology of these diseases as there was twenty years ago.¹ Disorders of the internal secretion which result in diabetes through involvement of the islands of Langerhans are more readily diagnosed.

Several reasons may explain the difficulties encountered in diagnosis: the location of the organ in the center of the body, which makes it inaccessible to palpation and surgery, and also inaccessible to securing the secretion through which to study the function of the organ, its structure and location, which make it inaccessible to the roentgen ray, and the fact that it is not often studied at necropsy, probably because of the early postmortem autolysis.

PATHOLOGY

There has been a gross exaggeration concerning the infrequency of pancreatic disease, owing to this difficulty in diagnosis, and also to the fact that the disease is not looked for because of the assumption of its rarity.

Mayo-Robson and Cammidge² furnish statistics that show more than 2 per cent of lesions of the pancreas in a series of 6,708 necropsies. They state that postmortem figures in relation to the pancreas are not reliable, because of the rapid autolytic changes taking place soon after death with the result that many lesions remain unrecognized.

The records of all necropsies performed in the department of pathology at the University of Minnesota Medical School, from Jan 1, 1919, to Sept 10, 1924, were examined, and seventy-three cases of gross lesions in the pancreas were found. The total number of necropsies for this period was 3,437, of which about 200 were of stillbirths and new-born infants. The percentage of pancreatic

1 Fallon, M. F. Relation of Gallstones to Pancreatitis, Boston M & S J 190 545-549 (March 27) 1924

2 Mayo-Robson and Cammidge. The Pancreas Its Surgery and Pathology, Philadelphia, W. B. Saunders Company, 1907, p 126

disease, in this series, is therefore 23 per cent, a result quite similar to that quoted by Mayo-Robson and Cammidge. The card index was used to find pancreatic diseases in the postmortems prior to 1919. Twenty-two additional cases were compiled in this group, making a total of ninety-five cases studied.

The classification of lesions quoted by Mayo-Robson and Cammidge is as follows: Total number of diseases of pancreas found, 142, tumors (primary and secondary), 55, atrophy or cirrhosis, 45, fatty changes, 9, hemorrhage, 3, calculi, 3, cysts, 2, hydatidiform cysts, 1, tuberculosis, 4, abscesses, 3, and miscellaneous, 17.

The types of lesions found, in our series, are as follows: Primary carcinoma, 29, melanoma, 1, metastatic carcinoma, 26, chronic pancreatitis, 14, acute pancreatic necrosis, 8, pancreatic lithiasis, 3, traumatic rupture, 4, gangrenous pancreatitis, 2, cyst, 1, hemochromatosis, 1, apoplexy, 1, pancreatic arteriosclerosis with coronary sclerosis, 3, pancreatic arteriosclerosis with sclerosis of kidney and hypertension, 1, and infarction, 1.

Of the primary carcinomas, twenty-two were in men and seven in women. The ages were distributed as follows: Between 38 and 39, three; 40 and 49, three; 50 and 59, twelve; 60 and 69, seven; and 70 and 79, four.

Eighty per cent were therefore above the age of 50.

Metastases were present in twenty-four cases, distributed as follows: Liver, 20, lymph nodes, 10, lungs, 6, kidney, 4, suprarenal, 3, stomach, 2, gallbladder, 2, heart, 1, and miscellaneous, 5.

Jaundice was present in eleven cases, gallstones in four, the liver was markedly enlarged in nine, the gallbladder enlarged, without stones, in three.

In the twenty-five cases of secondary carcinomas of the pancreas found, the primary locations of the tumor were as follows: Stomach, 19, rectum, 2, duodenum, 2, liver, 1, ovaries, 1, and mediastinal sarcoma, 1.

Of those originating in the stomach, sixteen were in men and three in women. Of this group, gallstones were present in only one case. The age distribution was as follows: Between 30 and 39, two; 40 and 49, three; 50 and 59, four; 60 and 69, seven; and 70 and 79, three.

Seventy-four per cent of the cases were therefore above the age of 50.

As will be seen from the foregoing, the pancreas is frequently the site of metastatic tumors, especially from the stomach. Of twenty-six cases, nineteen were secondary to gastric carcinoma. Of these, there was a remarkable preponderance of men over women, a ratio of more than five to one. The age incidence of the gastric carcinoma is very similar to that of the pancreatic carcinoma, that is, 74 per cent

occur after the age of 50. One case of metastatic tumor occurred in a young man, aged 22, in whom the primary carcinoma was in the liver.

Gallstones were present in five cases of chronic pancreatitis, in four cases of acute pancreatic necrosis, in one case of pancreatic stone, and in one case of cyst of the pancreas. These figures present a much higher percentage of gallstones associated with inflammatory lesions of the pancreas than with carcinomas. The percentage of gallstones with primary carcinoma is found to be higher than in secondary carcinoma. Such relationship between lesions of the gallbladder and the primary lesions of the pancreas seems to be more than accidental. Jaundice was present in four cases of chronic, and in one case of acute pancreatitis. Masses were palpable in the epigastrium in one case of chronic and in two cases of acute pancreatitis.

Tumors.—Primary neoplasms constitute the most important single group of pathologic conditions involving the pancreas. Benign tumors are rare. Schneider³ reports two cases of adenoma in addition to mentioning thirteen cases in the literature. In our series, not a single case of benign tumor was found. Of thirty-one cases of primary tumors, twenty-nine were carcinomas, one melanoma and one lymphosarcoma. Pancreatic tumors other than carcinomas are therefore negligible.

Involvement of the head of the pancreas is most frequent. In a large percentage of cases, this condition is accompanied either in the earlier or in the later stages by the development of jaundice, which is often of an intensity that is almost pathognomonic. The gallbladder not infrequently is greatly distended in this type of obstruction in contrast to its shrunken size in cases of gallstone jaundice. It may be large and palpable even in the absence of jaundice. The principal symptoms are indigestion, weakness, progressive loss of weight, anorexia, nausea, vomiting and pain. In our series, about 50 per cent had gastric distress with nausea and vomiting, and in about 20 per cent tumor masses could be palpated in the epigastrium. Pain is very common. It is often referred to the lower dorsal or lumbar region and to the angle of the left scapula. Itching is often intense when jaundice is present, as it was in a case which will be referred to later. Gilbride,⁴ however, found an absence of itching, in his series of cases of malignant disease. Although the jaundice is usually progressive, occasionally it may clear up after a time, only to recur. In one of the cases studied, the jaundice had completely cleared up for a period of two months.

³ Schneider, Helene. Adenoma of Islands of Langerhans (Insulinoma). Rev med de la Suisse Rom **44** 222-238 (April) 1924.

⁴ Gilbride, J. J. Tumors of the Pancreas. Operations Performed on Twelve Patients, J. A. M. A. **83** 984-989 (Sept 27) 1924.

The liver very frequently becomes enlarged during some stage of the disease, while it may later shrink to even less than normal in size

In our series, the ages range between 38 and 75, 80 per cent occur in those over 50, the largest number occurring between 50 and 60. There is a great preponderance of men over women, which, in our series, is in the ratio of more than three to one.

The duration of the disease ranges from two weeks to four years. The presence of glycosuria was not mentioned in the protocols, except in a few instances. The clinical diagnosis was given in only nine cases, and of these three were diagnosed as carcinoma of the stomach, two as carcinoma of the colon, three as carcinoma of the liver, and only two as carcinoma of the pancreas.

Acute Pancreatic Necrosis—This is a severe acute disease of the pancreas, often called acute hemorrhagic pancreatitis. The hemorrhagic, gangrenous and suppurative forms merely represent different stages in the same pathologic process, which begins with necrosis of the pancreas. The mortality of the disease is very high, variously estimated at 70 per cent, and only a very early surgical intervention may bring the mortality to a lower figure. In our series, there were eight cases of this lesion.

The symptoms of acute pancreatic necrosis are such as generally lead to erroneous diagnoses, such as perforating peptic ulcer, gallbladder disease, acute intestinal obstruction, kidney stone and angina pectoris. Usually, an operation or a postmortem examination establishes the correct diagnosis. The patients attacked are generally of middle age, in our series ranging principally between 30 and 50.

The urine should be repeatedly examined for sugar in such attacks. Rodriguez⁵ reports a striking case of severe symptoms in a woman presenting no sugar in the urine, but in whom, three days later, there was a marked glycosuria with 0.6 per cent blood sugar and abundant acetone and diacetic acid. The patient died in diabetic coma. At necropsy, acute hemorrhagic pancreatic necrosis with suppuration was found.

Chronic Pancreatitis—In our series, there were almost twice as many cases of chronic pancreatitis (fourteen cases) as of acute. There are two forms of chronic pancreatitis, the interlobular, characterized by overgrowth of connective tissue between the lobules, and the interacinar, in which fine bands of connective tissue are scattered between the acini, with more or less atrophy of the gland. In many of these there is present a definite sclerosis of the arteries. When the

⁵ Rodriguez, Juan. Acute Pancreatitis with Fat Necrosis Complicated by Diabetic Coma, J A M A 82: 203-204 (Jan 19) 1924.

atrophy and degeneration involve not only the acini of external secretion but also the elements of the internal secretion, the islands of Langerhans, diabetes results. Intermittent attacks of glycosuria are rather frequent in these cases, and the importance of this finding cannot be overemphasized.

"Chronic pancreatitis" is found much more frequently by surgeons at operation than by pathologists at necropsies. The enlarged, firm head of the pancreas so often found by surgeons at operation and diagnosed as chronic pancreatitis is probably only edema, congestion and exudate of temporary duration. The relative "infrequency," on the other hand, as reported by pathologists at necropsies, may be explained by the fact that the pancreas is rarely carefully studied by them, the organ being dismissed after a casual gross inspection with the report "pancreas apparently normal." Sections of the gland are seldom made. The early autolysis of the pancreas, often within a few hours postmortem, undoubtedly contributes to the carelessness of pancreatic postmortem pathology. It is not unlikely that many and various affections of the gland thus remain unrecognized.

Pancreatic Calculi.—Stones of the pancreatic duct are very rare, in our series of more than 3,000 necropsies, only three such cases were encountered. One of these has already been reported in detail in a previous communication.⁶ Kretz⁷ found only one case in 3,000 necropsies, and Simmonds,⁸ one in 2,000. The symptoms of pancreatic stone often closely resemble gallstone colic, but the presence of glycosuria during or immediately following some of the attacks is very helpful for a differential diagnosis. Lanceraux⁹ states that temporary glycosuria accompanies each attack of colic. This is undoubtedly an exaggeration. Still, Kinnicutt¹⁰ strongly emphasizes the importance of glycosuria accompanying the attacks of pain as a diagnostic sign differentiating attacks of pancreatic stones from those of gallstone.

The finding of sugar in the urine at various intervals was greatly relied on in the diagnosis of a case reported below. The symptoms at times may be vague, with pain in the epigastrium of different degrees of severity, sometimes agonizing in character, associated with vomiting. The attacks bear no relation to the kind of food or the time of meals.

⁶ Barron, M. The Relation of the Islets of Langerhans to Diabetes, with Special Reference to Cases of Pancreatic Lithiasis, *Surg., Gynec. & Obst.* **31** 437-448 (Nov.) 1920.

⁷ Kretz, R. *Handb. d. allg. Path.* **2**, 1913, cited by Pratt. *Diseases of the Pancreas*, Oxford Medicine, Oxford University Press, **3** 473, 1921.

⁸ Simmonds, M. Pancreatic Lithiasis, *Fortschr. a. d. Geb. d. Rontgenstrahlen* **30** 81 (Jan. 15) 1923.

⁹ Lanceraux, E. *J. de méd. int.*, February, 1889.

¹⁰ Kinnicutt, F. T. Pancreatic Lithiasis, with Report of a Case, *Am. J. M. Sc.* **124** 948-956 (Dec.) 1902.

Lazarus¹¹ reports approximately 50 per cent of cases of diabetes associated with pancreatic stone in the eighty cases that he compiled from the literature. This fact again emphasizes the importance of glycosuria.

Cysts—Cysts of the pancreas are about as rare as pancreatic stone, only one cyst being found in our series. Pathologically, they may be classified as (1) neoplastic cysts (cyst adenomas), (2) retention cysts and (3) pseudocysts. The last group is the most common. The pseudocyst generally arises through the collection of blood or the production of secretion and digestion in the lesser peritoneal cavity. An attack suggestive of acute pancreatic necrosis or a history of trauma frequently precedes the cyst formation. Pain is the chief symptom. Glycosuria is uncommon. When there is a fluctuating tumor in the epigastrium a little to the left of the midline, with a history as before stated, a diagnosis can readily be made. These cysts generally develop rapidly, in contrast to true cysts, which develop slowly.

Hemachromatosis—Hemachromatosis, or bronze diabetes, is a very rare condition due to a disorder of metabolism of carbohydrate and iron pigment associated with a sclerosis of the pancreas and other glands in the body, together with a deposition of pigment in various tissues and organs. The diagnosis can readily be made when the triad of symptoms, pigmentation of the skin, hepatic enlargement and glycosuria, is present. The diabetes associated with the pigment cirrhosis of the pancreas is probably neither the cause nor the result of the pigment anomaly. The causative factor of the disturbed pigment metabolism is probably also the cause of the diabetes. In our series, there was only one instance of this disease.

Apoplexy of the Pancreas—Apoplexy of the pancreas is extremely rare, so rare that some authors deny its existence. The lesion, in this condition, consists of a massive hemorrhage into the pancreas without any evidence of pancreatic necrosis or other pathology except the sclerosis of the pancreatic blood vessels. The case, in our series, was that of a man, aged 47, who had had advanced hypertension associated with severe headaches and poor vision due to retinal hemorrhages extending over a period of four years. There was albumin in the urine and reduced renal function. About two weeks before death, there was a sudden attack of severe abdominal pain with backache, nausea and vomiting. The blood sugar ranged between 0.12 and 0.18 per cent. At necropsy, there was the usual hypertension heart and a very extensive hemorrhage into and around the pancreas. The hemorrhage extended retroperitoneally to such an extent that intestinal obstruction

¹¹ Lazarus, P. Beiträge zur Pathologie und Therapie der Pankreaserkrankungen mit besonderer Berücksichtigung der Cysten und Steine, Ztschr f klin Med **51** 95, 203, **52** 381, 521, 1921.

was produced in two places through pressure. The blood clot in the pancreas itself showed various ages in its formation, suggesting slow bleeding. The pancreatic blood vessels showed atherosclerosis and rupture. This condition is entirely analogous to cerebral hemorrhage.

Pancreatic Arteriosclerosis.—A condition which I believe of great clinical importance and which is very little mentioned in textbooks or in the literature, but which may be noted in careful clinical studies, is the rather frequent association of glycosuria and true diabetes in cases of angina pectoris and other types of coronary sclerosis. In our postmortem series, careful studies of the pancreas were noted in three cases of coronary sclerosis, and in these advanced atherosclerosis of the pancreatic arteries was found. In another case of advanced hypertension with arteriosclerotic kidneys, similar changes were found.

When one remembers that one of the types of pathologic changes in the pancreas associated with diabetes is the atrophy of the parenchyma including the islands of Langerhans, as a result of atherosclerotic changes in the blood vessels, it is not surprising that the foregoing relation should obtain. From clinical observations, one is led to conclude that this association of lesions could be demonstrated at necropsies more frequently if more careful histologic studies of the pancreas were made.

The following cases are cited in detail to illustrate the difficulties encountered in arriving at correct diagnoses in cases of carcinoma of the pancreas, pancreatic lithiasis and chronic pancreatitis. Two of these cases, besides having been studied by me, were also studied in one of the leading clinics in the country as well as by a number of physicians.

REPORT OF CASES

CASE 1—A. W., a man, aged 45, married, a merchant, when first seen by me, April 8, 1922, complained of pains in the back radiating forward into the abdomen of about five or six weeks' duration, constipation, gradual loss in weight and progressive weakness. About five months before, he had been refused insurance because of diabetes, for which he was treated by a diabetes specialist for several months.

The previous history and the family history were entirely negative. The usual weight was 205 pounds (93 kg.), the present weight, 186 pounds (84.4 kg.). Constipation had developed six weeks before. He had been awakened at night by severe pain in the upper part of the abdomen radiating to the back. The principal complaint at the time of examination was backache, at times dull, at other times sharp, which radiated into the epigastrium. There was no nausea or vomiting. Recently, he had had sharp, shooting pains into the left knee and a dull pain with fulness in the abdomen.

Physical examination was entirely negative except for a facial expression of severe distress. Deep percussion over the lower dorsal vertebrae produced pain deep in the epigastrium.

Frequent examinations of the urine showed a small amount of sugar present on two different occasions. While under treatment for diabetes, sugar had been found only five or six times. Examination of the feces and stomach

contents was negative. Because of the persistence of severe pain in the back, a spinal puncture was done. The spinal fluid was negative to all tests. Roentgen-ray studies showed no gastric or duodenal lesions.

Blood sugar estimations gave peculiar results. One examination showed 0.13 per cent. An examination following a rather severe attack of pain gave 0.19 per cent, with a trace of sugar in the urine. A test one month later gave 0.13 per cent.

Because of the history of glycosuria and the essentially negative findings on physical examination, together with the rather erratic sugar findings, both in the urine and the blood, which had no definite relation to the food intake, the probable diagnosis of pancreatic disease suggested itself. A corroboration could not be found in the examination of the stools for excess of fat or undigested muscle fibers. A sugar tolerance curve gave essentially normal results.

In the course of the observation, the patient was seen by a large number of prominent physicians without a definite diagnosis being arrived at. Because of no improvement in his condition, he visited one of the large clinics on two different occasions, when very careful studies were made. They found no definite organic lesions, and concluded that the symptoms were largely due to the neurotic condition of the patient.

The following are a few extracts from my clinical notes on this case:

April 11, there was a severe, gnawing pain in the back, worse on sitting.

May 1, the weight was 182 pounds (82.6 kg), the condition was worse.

May 29, the pain was still more intense, the weight was 168 pounds (76.2 kg).

June 28, the pain was more cramp-like in character, the weight was 172 pounds (78 kg).

July 11, the weight was 176 pounds (79.8 kg). The patient had had agonizing attacks of pain, the urine showed sugar present.

July 11, after two weeks at some mud baths, he returned without relief. The weight was 166 pounds (75.3 kg). There was an icteric tinge to the conjunctiva and skin, tenderness in the epigastrum, and considerable bile in the urine. A diagnosis of carcinoma of the pancreas was now definitely made and an exploration advised. Operation showed the head of the pancreas large, nodular and cartilaginous, corroborating the diagnosis of carcinoma of the head of the pancreas. The gallbladder was markedly distended, there were no gallstones.

The patient failed rapidly, the skin became intensely greenish-brown, and itching was very marked. He became very emaciated, the liver enlarged to below the umbilicus, then receded again. The patient died, Jan 18, 1923.

In this case, the early disturbance of the pancreas by carcinoma was manifested by glycosuria. This is less common in carcinomas than in other affections, but nevertheless does occur. Though Joslyn well points out that every case of glycosuria should be considered as diabetes until proved otherwise, every case of glycosuria should not be *treated* as diabetes unless diabetes can be established by further appropriate tests and observations. The irregular and variable sugar levels in the blood on a constant diet and the inconstant presence of sugar in the urine, together with the normal sugar tolerance curve, indicated a disturbance of the pancreas other than true diabetes.

CASE 2—B.B., a man, aged 55, married, when first seen, Dec 26, 1923, complained of marked weakness, loss of 20 pounds (9 kg) in weight, attacks of pain and fulness in the epigastrum. The illness was of three months' duration. The family and the past histories were negative. About one year before, he had developed backaches, which lasted for a day or two.

About the middle of September, he developed severe pains, stabbing in character, in the lower part of the right side of the chest, radiating to the right hypochondrium. He was examined in a clinic and the condition diagnosed as probable gallstones. In the latter part of November, he was examined in one of the leading clinics in the country, complete physical and laboratory

examinations led to the diagnosis of probable pleurisy and questionable gallbladder, with no indications for an operation. A roentgen-ray examination of the chest showed a thickened pleura at the right base.

After returning home, he developed a number of very severe attacks of cramps in the upper part of the abdomen, many of them sharp and stabbing in character, lasting from one to three days. He was very ill during the attacks, but between attacks he felt well, except for weakness. About the middle of December, he had a severe attack of pain in the left side of the upper part of the chest anteriorly, lasting one day. During some of the attacks, he would perspire so freely as to drench the bedclothes.

Physical examination showed Temperature, 99.4 F., pulse, 94, and respiration, 28. There was definite evidence of loss in weight and marked tenderness in the right epigastric region, but nothing palpable. Deep percussion over the lower dorsal spine produced pain in the epigastrium.

The urine showed three plus sugar. On the following day, sugar was absent. Blood examination showed 37 per cent hemoglobin and 11,600 leukocytes. The stomach contents and the stools were entirely normal.

December 28, the leukocyte count was 4,900 and blood sugar 0.123 per cent.

December 29, the urine showed no sugar in the morning specimen, 2 per cent in the evening specimen.

January 17, the patient was improved, the weight was 164 pounds (74.4 kg.).

February 22, a large, tender mass was palpable in the right hypochondrium, conforming to the liver outline.

March 7, the liver was not palpable.

March 26, the patient had a severe attack of backache, cramps, vomiting and chills. There was a mass in the gallbladder region the size of a hen's egg, and an icteric tinge of the conjunctiva. The urine showed 16 per cent sugar, urobilin, urobilinogen and a trace of bile. The fasting blood sugar, two days later, was 0.242 per cent.

April 19, the patient had another severe attack of cramps in the lower part of the abdomen.

May 16, there was definite jaundice of the skin with itching, the liver was large, reaching 8 cm below the costal margin.

May 22, an exploratory operation showed a soft, mushy mass in the head of the pancreas, not at all suggestive of carcinoma. A cholecystostomy was performed for relief of jaundice. The patient died, four days later, from bronchopneumonia.

This case presents findings of unusual interest. During the first three days of study, the symptoms of colicky pain, deep in the epigastrium and back, together with erratic sugar curves in the urine, suggested very strongly the diagnosis of a lesion in the head of the pancreas, probably stone with acute suppurative pancreatitis. With this diagnosis, the patient was referred back to the clinic, December 29, with the recommendation that an exploratory operation be performed. After repeated examinations, the opinion was that there was insufficient evidence for an operation.

The presence of sugar was generally associated with the severe attacks. The glycosuria was more of a true alimentary glycosuria because its appearance always followed immediately after a heavy meal, and it disappeared in the morning. It ranged from 0.5 to 3 per cent in amount, quantities far in excess of that found in renal diabetes. Urobilin and urobilinogen were definitely associated with the recurrence of attacks. Bile was found only on two occasions following attacks of unusual severity. When the bile appeared in the urine together with the icteric tinge of the skin, the diagnosis of a lesion in the head of the pancreas was felt to be well established. The enlargement of the gallbladder on several occasions aided in this assumption. Because of the severe colicky attacks, not unlike those of gallstone colic, the most probable diagnosis was pancreatic stone. The slight temperature and increased leukocyte count with several of the attacks suggested an inflammatory condition in the pancreas.

When the exploratory operation was performed, a large tumor mass, mushy in consistency, was found involving the head of the pancreas. Although the mass was not explored at the time of operation, the gross description by the surgeon coincided with the gross description of surgical cases reported in the literature, in which the necropsies showed that the mass was a result of severe, acute inflammation surrounding stones in the pancreatic duct.

Korte¹² reports a case presenting symptoms of biliary colic. The patient was operated on, gallstones were removed and the gallbladder was drained. Shortly after the operation, similar attacks occurred. The patient died. At necropsy, a large tumor was found in the head of the pancreas which at first was thought to be malignant, but on examination proved to be a diffuse abscess surrounding pancreatic stones.

Delageniere¹³ reports the case of a man, aged 59, who developed violent epigastric pain followed by increasing jaundice. At operation, the distended gallbladder was opened and a stone removed. The head of the pancreas was large, soft and infiltrated. On incision, calculi were found in the ducts. These were removed, drainage inserted, and the patient recovered.

Although permission for a postmortem was not obtained in the case under discussion, the clinical history as outlined, together with the peculiar mass found at operation in the head of the pancreas, points quite definitely to the diagnosis of pancreatic lithiasis with acute suppurative pancreatitis, the diagnosis originally made when the patient was first seen about six months before his death. In this case also, the principal basis for diagnosis was the peculiar course of glycosuria and blood sugar levels.

CASE 3.—Mrs. S. R., aged 64, was referred to me with a diagnosis of severe constipation and diabetes of several years' duration. The present illness started twelve years before with sudden pain in the abdomen and temporary inability to move the bowels, cathartics caused painful evacuations. The first attack lasted for two weeks, and was followed by frequent attacks. The patient now complained of pain in the left side in the lower part of the abdomen, aching and piercing in character, which radiated to the back on the left side and, at times, into the left hip and left knee. She also complained of constipation and loss of appetite.

Physical examination revealed a large mass freely movable in the lower left quadrant. The stools showed an irregular mass, suggesting stenosis along some part of the bowel. Examination of about thirty specimens of urine showed sugar present, from a barely recognizable trace to 17.5 gm. in twenty-four hours, in about 50 per cent of the specimens. So irregularly did the sugar appear in the urine that it was necessary to resort to special sugar tests to establish the identity of the reducing body. The Cammidge test was performed on a number of specimens, and was found positive in most instances.

A diagnosis of diabetes could not be made because of the inconstancy of the urinary findings on a rather constant diet. Because of the evidence of partial obstruction of the bowels, a laparotomy was performed and a diverticulitis of the colon was found, with an inflammatory mass uniting the sigmoid to the body of the uterus. The patient died the day following the operation. At necropsy, an advanced, chronic interstitial pancreatitis was found, with dense bundles of connective tissue permeating the organ. This case was complicated by two unrelated conditions being present, but the interesting feature was the spasmodic appearance of sugar in the urine, which was not in accord with the ordinary course of diabetes, but for which no true explanation was found. It also is interesting to note that a pancreatic disturbance was suggested by the pathologist examining the specimens of urine.

12 Korte Berl Klinik, December, 1896.

13 Delageniere, H. De la choledoctomie retropancreatique, pour calculs enclavés dans la portion retropancreatique du choledoque, Arch prov de chir 15 505-515, 1906.

CONCLUSIONS

- 1 Pancreatic disease is more common than is usually supposed
- 2 Diseases of the pancreas are diagnosed with difficulty because of its inaccessibility to palpitation, to roentgen-ray studies, to reliable functional tests and to surgical intervention
- 3 From postmortem statistics, primary carcinoma is the most common lesion of the gland, with secondary carcinoma, chronic pancreatitis and acute pancreatic necrosis following respectively in order of frequency
- 4 Careful studies of the urine for sugar and of the blood for changes in sugar levels and atypical sugar tolerance curves are valuable in diagnosis
- 5 Postmortem pathology of the pancreas is generally rather superficial, probably owing to the rapid postmortem changes
- 6 Apoplexy of the pancreas is a clinical entity, though rare
- 7 Pancreatic atherosclerosis is probably a relatively common condition associated with cases of advanced hypertension and with coronary sclerosis. The diabetes so frequently encountered, in these cases, is probably due almost entirely to this lesion
- 8 Diabetes mellitus should always be suspected, but should not be definitely diagnosed from the mere presence of sugar in the urine until appropriate tests are made to establish the diagnosis
- 9 No syndrome is pathognomonic of pancreatic disease, one can arrive at the correct diagnosis only through a combination of all the findings

Book Reviews

THE THEORY AND PRACTICE OF MEDICAL SOCIAL WORK By EDNA G HENRY,
Social Service Department, Indiana University Pp 195 Ann Arbor, Mich
Edward Brothers, 1924

Medical social service has been assuming a position of increasing importance in the last few years until it has become an indispensable adjunct to diagnosis, treatment and teaching. It supplies to the clinician the intimate contact with the daily life and social conditions of the patient which is held by the family physician, and without which, while he may diagnose and treat the disease, he cannot "treat the patient". A clinician in a psychiatric clinic recently stated that diagnosis in the clinic had improved 20 per cent since the organization of their social service department.

Medical social work must always remain much of an art to be gained by experience, but its methods and aims are scientific, and these may be formulated in a text, as well as the general methods of procedure and the results of the experience of the author.

There has been a very definite need of texts on medical social work, not only for the medical social worker but also for the clinician, hospital and dispensary executives and medical students. This need is met in a large part by the present volume and could be filled by it most successfully if a more detailed consideration were given to certain aspects. This the author is especially well fitted to do.

The purpose and aims of medical social work are well stated, but many of the problems are little more than mentioned, and not enough space is given to suggestions as to procedure. The subject of industrial accidents and diseases is allowed only one-half page, too little to offer much in the way of guidance. Such problems as convalescent care, vocational guidance and training, are properly the functions of special organizations, still they are problems for the solution of which the medical social worker is immediately responsible and should be considered in some detail. In places some suggestions as to procedure are given. This is true of the section on illegitimacy, although the course outlined might be thought more dogmatic than is justifiable. Many social workers have found it very inadvisable for the unmarried mother to keep the child. For the guidance of the student worker both aspects should be considered.

It is hoped that the present volume will have such success that the author and publishers will feel justified in getting out a revised and enlarged edition.

DIABETIC DIET A HANDBOOK FOR DIABETICS By H DORIS McHENRY, B A,
and MARJORIE M COOPER, B A, with a preface by J A GILCHRIST, B A,
M B, and F G BANTING, M C, M B, MRCS, FRCP, MD, D Sc,LLD
New York Harper and Brothers, 1925

Little "instructor" books for diabetics are almost all following a definite form. The task of teaching diabetic patients how to prepare their own menus is not an easy one, the danger of telling too much is as great as the danger of telling too little. In this book too little is told—the instructions for planning diets seem quite inadequate to reach more than the intelligent patients. Tables of equivalent food values, too, are lacking. The recipes are good.

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